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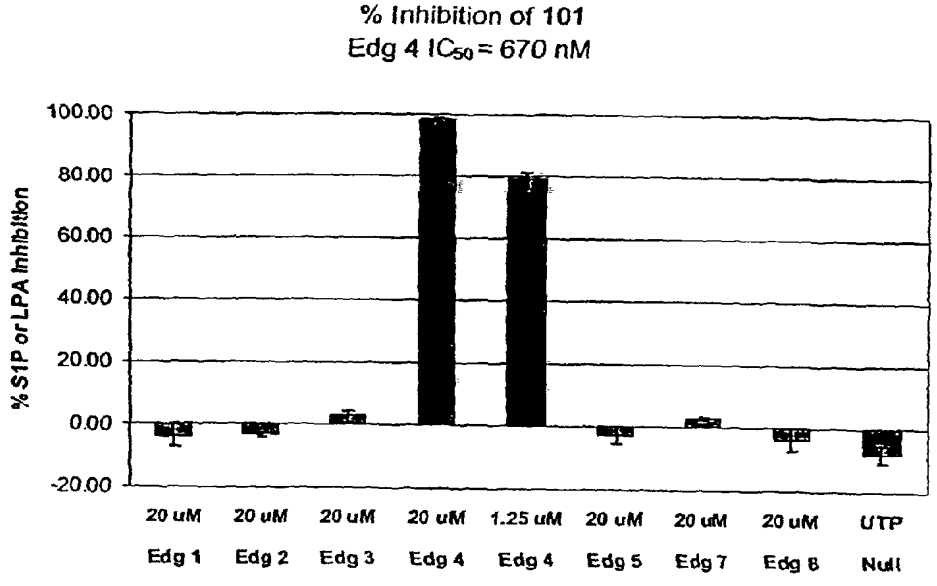
(54) Title: METHODS OF TREATING CONDITIONS ASSOCIATED WITH AN EDG RECEPTOR



(57) Abstract: The present invention provides a method of modulating an Edg-2, Edg-3, Ed-4 or Edg7 receptor mediated biological activity in a cell. A cell expressing the Edg-2, Edg-3, Edg-4 or Edg 7 receptor is contacted with a modulator of the Edg-2, Edg-3, Ed-4 or Edg 7 receptor sufficient to modulate receptor mediated biological activity. In another aspect, the present invention provides a method for modulating an Edg-2, Edg-3, Ed-4 or Edg-7 receptor mediated biological in a subject. A therapeutically effective amount of a modulator of the Edg-2, Edg-3, Ed-4 or Edg7 receptor is administered to the subject.

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METHODS OF TREATING CONDITIONS ASSOCIATED WITH AN EDG RECEPTOR

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of priority of U.S. Provisional Application Nos. 60/350,445, 60/350,446, 60/350,447, 60/350,448, all filed January 18, 2002, the contents of which are hereby incorporated by reference in their entireties.

1. FIELD OF INVENTION

The present invention relates generally to methods of modulating biological activity mediated by an Edg-2, an Edg-3, an Edg-4 or an Edg-7 receptor. More specifically, the present invention provides compounds and compositions, which may be used to selectively modulate, *e.g.*, antagonize an Edg-2, an Edg-3, an Edg-4 or an Edg-7. The present invention also provides methods for making these compounds.

2. BACKGROUND OF THE INVENTION

Recent studies have revealed a complex biological role for cell membrane phospholipids, which were previously believed to have only a structural function. Following cell activation, membrane phospholipids may be metabolized to eicosanoids and lysophospholipids, which are important regulators of cellular function and behavior. Lysophospholipids include compounds such as lysophosphatidic acid ("LPA"), sphingosine-1-phosphate ("S1P"), lysophosphatidylcholine and sphingosylphosphorylcholine and are important second messengers that can activate particular cell surface transmembrane G-protein coupled receptors known as endothelial gene differentiation ("Edg") receptors.

Two quite distinct subfamilies of GPCRs bind LPA and S1P specifically and transduce diverse cellular signals by associating with one or more G proteins. Based on amino acid sequence identities, S1P1 (Edg 1), S1P3 (Edg 3), S1P2 (Edg 5), and S1P5 (Edg 8) belong to one structural cluster and LPA1 (Edg 2), LPA2 (Edg 4) and LPA3 (Edg 7) are members of a second structural cluster (Goetzl, B. J., and Lynch, K. R. **2000**, *Ann. N. Y. Acad. Sci.* 905:1-357). Members of both subfamilies range in size from 351 to 400 amino acids, and are encoded by chromosomes 1, 9 or 19. The amino acid sequence of S1P4 (Edg 6) lies between those of the two major clusters by

amino acid sequence identity (Graler *et al*, **1998**, *Genomics 53,* 164-169). Edg-6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. (Graler *et al*, **1998**, *Genomics 53,* 164-169). Currently, there are three known Edg receptors specifically activated by LPA (LPA1 or Edg 2, LPA2 or Edg 4 and LPA3 or Bdg 7) and five known S1P receptors specifically activated by S1P (S1P1 or Edg 1, S1P2 or Edg 5, S1P3 or Edg 3, S1P4 or Edg 6, and S1PS or Edg 8).

Edg-1 (human Edg-1, GenBank Accession No. *AF233365),* Edg-3 (human Edg-3, GenBank Accession No. X83864), Edg-5 (human Edg-5, GenBank Accession No. AF034780), Edg-6 (human Edg-6, GenBank Accession No. AJ000479) and Edg-8 (human Edg-8, GenBank Accession No. AF3 17676) receptors are activated by S1P, while LPA activates Edg-2 (human Edg-2, GenBank Accession No., U78 192), Edg-4 (human Edg-4, GenBank Accession Nos. AF233092 or AFO1 1466) and Edg-7 (human Edg-7, GenBank Accession No. AF127 138) receptors. Although, all three LPA receptors *(i.e.,* Edg-2, Edg-4 and Edg-7) bind LPA, compounds, which discriminate between these receptors have been identified (Im *et al,* 2000, *Mol. Pharmacol.* 57 (4):753-759). Further, Edg 2, Edg-4 and Edg-7 appear to exhibit significant pharmacological differences (Bandoh *et al.,* 2000, *FEBS Lett.* 478:159-165).

Importantly, Edg receptors are believed to mediate critical cellular events such as cell proliferation and cell migration, which makes these receptors attractive therapeutic targets. However, currently known compounds, which bind to LPA, are almost exclusively phospholipids *(e.g,* LPA and S1P, analogs of LPA and S1P, dioctyl glycerol, *etc).* Most of these phospholipids compounds fail to effectively discriminate between different Edg receptors and have poor physicochemical properties, which limits their potential use as pharmaceutical agents. Thus, there exists a need for compounds, which are not phospholipids that bind or otherwise regulate Edg receptors and can also selectively bind to a specific Edg receptor.

3. SUMMARY OF THE INVENTION

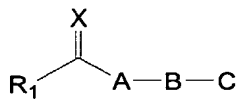
In a first aspect, the present invention addresses these and other needs by providing compounds that modulate the Edg-4 (LPA2) receptor *(e.g,* human Edg-4, GenBank Accession Nos. AF233092 or AFO1 1466). Such compounds preferably selectively bind or otherwise modulate the Edg-4 receptor.

The present invention provides methods for modulating (antagonizing or agonizing) Edg-4 receptor mediated biological activity. The present invention also provides methods for using Edg-4 modulators (antagonists or agonists) in treating or preventing diseases such as ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("AIRDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma, surface epithelial cell injury, *(e.g.,* transcorneal freezing or cutaneous bums) and cardiovascular diseases *(e.g.,* ischemia) in a subject in need of such treatment or prevention. Further, the present invention provides compounds and compositions that can, for example, be used in modulating Edg-4 receptor mediated biological activity or treating or preventing diseases such as those mentioned above. The present invention still further provides methods for synthesizing the compounds.

In one aspect, the present invention provides a method of modulating an Edg-4 receptor mediated biological activity in a cell. A cell expressing the Edg-4 receptor is contacted with an amount of an Edg-4 receptor modulator sufficient to modulate the Edg-4 receptor mediated biological activity.

In another aspect, the present invention provides a method for modulating Edg-4 receptor mediated biological activity in a subject. In such a method, an amount of of the Edg-2 receptor effective to modulate the Edg-2 receptor mediated biological activity is administered to the subject.

The present invention also provides compounds (agonists or antagonists) that modulate Edg-4 receptor mediated biological activity. The agonists or antagonists are compounds of structural formula (I) and can be utilized as part of the methods of the present invention:



(I)

or a pharmaceutically available solvate or hydrate thereof, wherein:

R_1 is hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylamino,

substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkylarylamino, substituted alkylarylamino, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylamino, substituted arylamino, arylalkyl, substituted arylalkyl, dialkylamino, substituted dialkylamino, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl sulfonylamino or substituted sulfonylamino;

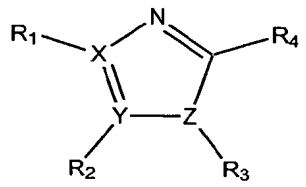
X= O or S;

A is NR_2, O or S;

R_2 is hydrogen, alkyl or substituted alkyl; and

B and C are independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (IV):

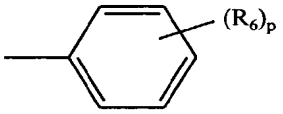


(IV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, $-(C_5\text{-}C_{10})$cycloheteroaryl, $-(C_3\text{-}C_6)$cycloheteroalkyl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle,

$-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-NR_5R_5$, $=NR_5$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_3-C_{10})cycloheteroalkyl(R_5)_m$, $-(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X and Y are each independently C or N; and

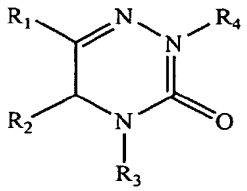
Z is O, S, C or N, wherein if Z is O or S, then R_3 is an electron pair;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_3 and R_4 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

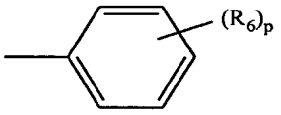
In another embodiment, the modulator is a compound of structural formula (V):



(V)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

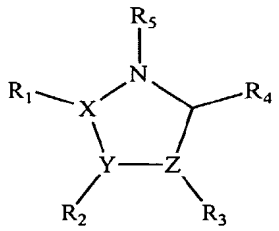
each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), $-CO_2(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1\text{-}C_{10})$alkyl, $-NHC(O)NH(C_1\text{-}C_{10})$alkyl, $-OC(O)(C_1\text{-}C_{10})$alkyl, $-OC(O)O(C_1\text{-}C_{10})$alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5; and

R_1 and R_2 or R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

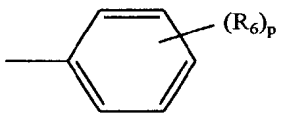
In yet another embodiment, the agonists or antagonists are compounds of structural formula (VI):



(VI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -indole, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

R_5 or R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X, Y and Z are independently O, S, C or N, wherein if X, Y or Z is O or S, R_1 is an electron pair;

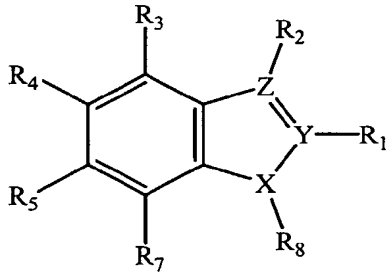
R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_1 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_4 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

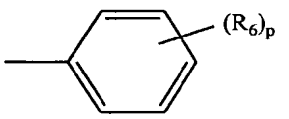
In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (VII):



(VII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

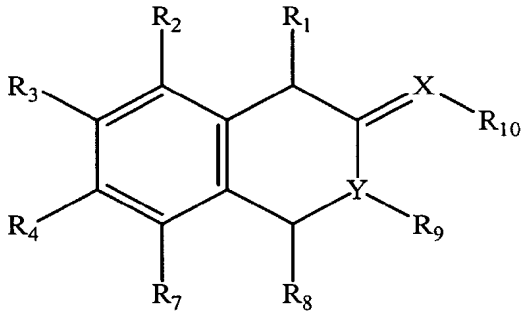
m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X is O, S, C or N, wherein if X is O or S, R_1 is an electron pair; and

Y and Z are independently N or C, wherein if Y or Z is N, R_1 and R_2 are each an electron pair.

In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (VIII):

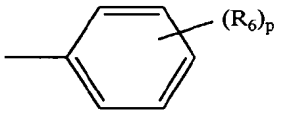


(VIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, $-(C_5-C_{10})heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$,

$-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

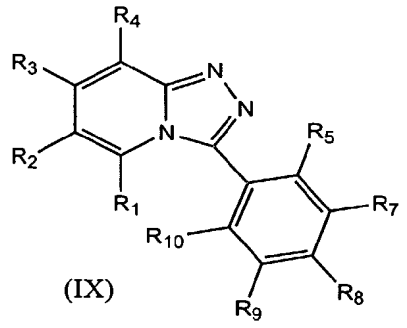
each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5; and

X and Y are independently O, S or N, wherein if X or Y is O or S, R_9 and R_{10} are an electron pair.

In yet another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (IX):

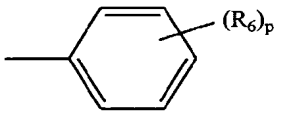


(IX)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$,

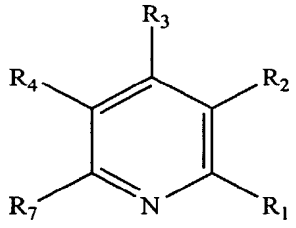
-C(O)NH(CH_2)$_m$(R_5), -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -(C_5-C_{10})heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, -$CO_2(CH_2)_mR_5$, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -(C_1-C_{10})alkylNHC(O)(CH_2)$_m$$R_5$, -($C_1$-$C_{10}$)alkyl$NR_5R_5$, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -$SR_5$, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -$CO_2(CH_2)_mCH((C_1$-$C_{10})alkyl(C_1$-$C_{10})alkyl)$, -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -$CO_2(CH_2)_m$(C_1-C_{10})alkyl, -$CO_2(CH_2)_mH$, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;
m is independently an integer ranging from 0 to 8; and
p is independently an integer ranging from 0 to 5.

In yet another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (X):

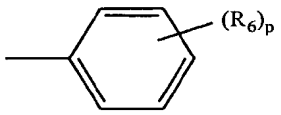


(X)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$,

$-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$, $-CO_2H$, $-(C_1-C_{10})$alkylC(O)NH$(CH_2)_mR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

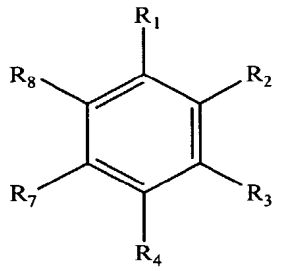
R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

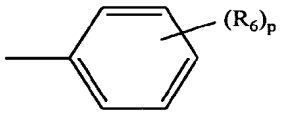
In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present are compounds of structural formula (XI):



(XI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, $-(C_5\text{-}C_{10})$cycloheteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), $-CO_2(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1\text{-}C_{10})$alkyl,

$-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

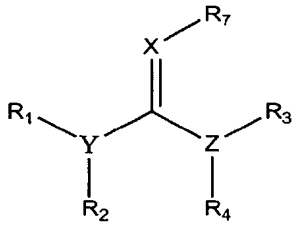
R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_7 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (XII):

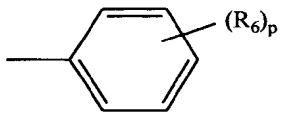


(XII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, $-(C_5-C_{10})$cycloheteroaryl, $-(C_3-C_6)$cycloheteroalkyl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-NR_5R_5$, $=NR_5$,

-(C_1-C_{10})alkylNHC(O)(CH_2)$_m$$R_5$, -($C_3$-$C_{10}$)cycloheteroalkyl($R_5$)$_m$, -($CH_2$)$_m$$R_5$, -($C_1$-$C_{10}$)alkylNR$_5R_5$, -OC(O)($CH_2$)$_mCHR_5R_5$, -$CO_2$($CH_2$)$_mCHR_5R_5$, -OC(O)OR$_5$, -SR$_5$, -S(O)R$_5$, -S(O)$_2R_5$, -S(O)$_2NHR_5$, or



wherein;

each R_5 or R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

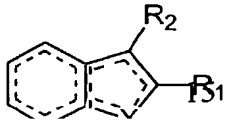
R_3 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring;

R_1 or R_2 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring; and

R_2 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring.

In a second aspect, the present invention provides compounds that modulate the Edg-7 (LPA3) receptor (e.g., human Edg-7, GenBank Accession No. AF127138). Such compounds selectively bind or otherwise modulate the Edg-7 receptor.

The compounds (agonists or antagonists) that can, for example, be used to modulate Edg-7 receptor mediated biological activity or to treat or prevent diseases such as those discussed above. The agonists or antagonists are compounds of structural formula (XIII) and can be utilized in the methods of the present invention:



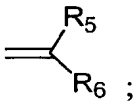
(XIII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

X is NR^3, S or O;

R_1 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, amino, carbamoyl, substituted carbamoyl, oxo, thiono or $-NR^4$; and

R_2 is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkyloxy, substituted alkyloxy, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or



;

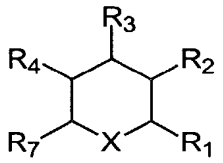
R_3 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl or substituted heteroalkyl;

R_4 is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, carbamoyl,

substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heteroaryl substituted heteroaryl, cycloheteroalkyl, substituted cycloheteroalkyl, and

R_5 and R_6 are independently hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or optionally along with the carbon to which they are attached form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

The present invention also provides compounds (agonists or antagonists) that can, for example, be used to modulate Edg-7 receptor mediated biological activity or to treat or prevent diseases such as those discussed above. The agonists or antagonists can be utilized in the methods of the present invention and are compounds of structural formula (XIV):

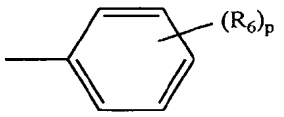


(XIV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5,

$-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

X is CH_2, C=O, O, S, SO_2, C, or NR_5;

R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

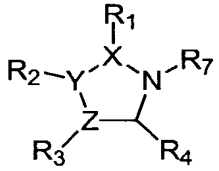
R_1, R_2, R_3 R_4 and R_7 can also be an electron such that when two groups are on adjacent carbon atoms they form a double bond;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

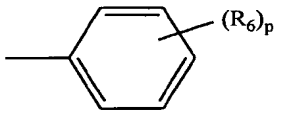
The agonists or antagonists can be utilized in the methods of the present invention and are also compounds of structural formula (XV):



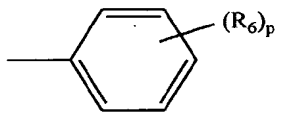
(XV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -heterocylcoalkyl, -$C(S)N(R_5)(R_5)$, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



R_3 is -H, -$C(R_5)_3$, -$(CH_2)_mOH$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -$N(C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl, -$O(C_1$-$C_{10})$alkyl, -$C(O)(C_1$-$C_{10})$alkyl, -$C(O)NH(CH_2)_m(C_1$-$C_{10})$alkyl, -OCF_3, -benzyl, -$CO_2(CH_2)_mCH((C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl), -$CO_2(C_1$-$C_{10})$alkyl, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl,

$-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

X, Y, and Z are each independently C=O, O, S, C, or N; wherein if X, Y, or Z is O or S, R_1 is an electron pair;

R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

The present invention provides methods for modulating Edg-7 receptor mediated biological activity. The present invention also provides methods for using Edg-7 modulators (*i.e.*, agonists and antagonists) in treating or preventing diseases such as ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("ARDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma, surface epithelial cell injury, (*e.g.*, transcorneal freezing or cutaneous burns) and cardiovascular diseases (*e.g.*, ischemia) in a subject in need of such treatment or prevention. Further, the present invention provides compounds and compositions for use in modulating Edg-7 receptor mediated biological activity or treating or preventing diseases such as those mentioned above as well as methods for synthesizing the compounds.

In one aspect, the present invention provides a method of modulating (antagonizing or agonizing) an Edg-7 receptor mediated biological activity in a cell. A cell expressing the Edg-7 receptor is contacted with an amount of an Edg-7 receptor modulator of the invention sufficient to modulate the Edg-7 receptor mediated biological activity.

In a second aspect, the present invention provides a method for modulating Edg-7 receptor mediated biological activity in a subject. In such a method, an amount of a modulator of the Edg-7 receptor of the invention effective to modulate the Edg-7 receptor mediated biological activity is administered to the subject.

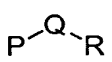
In a further aspect, the present invention provides compounds that modulate the Edg-2 (LPA1) receptor (*e.g.*, human Edg-2, GenBank Accession No., U78192). Such compounds preferably selectively bind or otherwise modulate the EDG-2 receptor.

In certain embodiments, the present invention provides methods for modulating (antagonizing or agonizing) Edg-2 receptor mediated biological activity. The present invention also provides methods for using Edg-2 modulators (agonists and antagonists) in treating or preventing diseases such as ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("ARDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma, surface epithelial cell injury, (*e.g.*, transcorneal freezing or cutaneous burns) and cardiovascular diseases (*e.g.*, ischemia) in a subject in need of such treatment or prevention. Further, the present invention provides compounds and compositions that can, for example, be used in modulating Edg-2 receptor mediated biological activity or treating or preventing diseases such as those mentioned above. The present invention still further provides methods for synthesizing the compounds.

In one aspect, the present invention provides a method of modulating an Edg-2 receptor mediated biological activity in a cell. A cell expressing the Edg-2 receptor is contacted with an amount of an Edg-2 receptor modulator sufficient to modulate the Edg-2 receptor mediated biological activity.

In another aspect, the present invention provides a method for modulating Edg-2 receptor mediated biological activity in a subject. In such a method, an amount of a modulator of the Edg-2 receptor effective to modulate the Edg-2 receptor mediated biological activity is administered to the subject.

The present invention also provides compounds (agonists or antagonists) that modulate Edg-2 receptor mediated biological activity. In certain aspects, the agonists or antagonists are compounds of structural formula (XX) and can be utilized as part of the methods of the present invention:

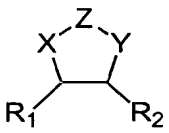


(XX)

or a pharmaceutically available salt, hydrate or solvate thereof wherein:

P, Q and R are independently aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl.

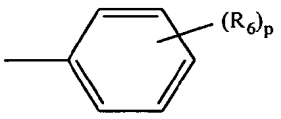
In other aspects, the agonists or antagonists can be utilized as part of the methods of the present invention and are compounds of structural formula (XXIII):



(XXIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each of R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl,

-C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

X, Y, and Z are each independently C(R_5)(R_5), C(O), O, C(S), S, C=N(R_5), or NR_3;

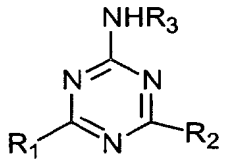
each m is independently an integer ranging from 0 to 8;

each p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and X or R_2 and Y can together form a double bond.

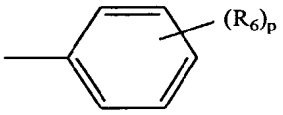
In other aspects, the agonists or antagonists are compounds that can be utilized as part of the methods of the present invention and are of structural formula (XVII):



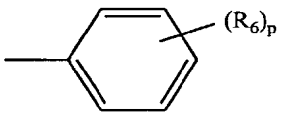
(XVII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, -NO_2, -CN, -C(R_5)$_3$, -(CH_2)$_m$OH, -N(R_5)(R_5), -O(CH_2)$_m$$R_5$, -C(O)$R_5$, -C(O)N$R_5$$R_5$, -C(O)NH($CH_2$)$_m$($R_5$), -$OCF_3$, -benzyl, -$CO_2$CH($R_5$)($R_5$), -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_5$)heteroaryl, -($C_6$)heteroaryl, -($C_5$-$C_{10}$)heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$$R_5$, -N(OH)aryl, -NHC(O)$R_5$, -NHC(O)O$R_5$, -NHC(O)N$HR_5$, -heterocylcoalkyl, -($C_1$-$C_{10}$)alkylNHC(O)($CH_2$)$_m$$R_5$, -($C_1$-$C_{10}$)alkylN$R_5$$R_5$, -OC(O)($CH_2$)$_mCHR_5$$R_5$, -$CO_2$($CH_2$)$_mCHR_5$$R_5$, -OC(O)O$R_5$, -S$R_5$, -S(O)$R_5$, -S(O)$_2$$R_5$, -S(O)$_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

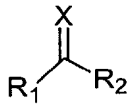
each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), $-CO_2(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1\text{-}C_{10})$alkyl, $-NHC(O)NH(C_1\text{-}C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1\text{-}C_{10})$alkyl, or $-SO_2NH_2$;

two R_6 groups on adjacent carbon atoms can also be joined to form a 5 or 6-membered acyclic or heterocyclic ring or a 6 membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

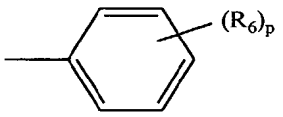
In yet other aspects, the agonists or antagonists are compounds of structural formula (XXV) and can be utilized as part of the methods of the present invention:



(XXV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -NH(aryl), -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, -aryl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_3-C_{10})$cycloalkyl(aryl), $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-N(OH)$aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

R_1 and R_2 can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In another aspect, the present invention provides compounds that modulate the S1P3 or Edg-3 receptor (e.g. human Edg-3, GenBank Accession No. X83864). Such compounds preferably selectively bind or otherwise modulate the Edg-3 receptor.

In one embodiment, the present invention provides methods for modulating Edg-3 receptor mediated biological activity. The present invention also provides methods for using Edg-3 modulators (*i.e.*, agonists or antagonists) in treating or preventing diseases such as ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("ARDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma, surface epithelial cell injury, (*e.g.*, transcorneal freezing or cutaneous burns) and cardiovascular diseases (*e.g.*, ischemia) in a subject in need of such treatment or prevention.

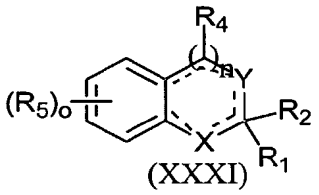
In a another aspect, the present invention provides methods for using Edg-3 modulators (*i.e.*, agonists or antagonists) in treating or preventing disorders such as, but not limited to, vasoconstriction in cerebral arteries, autoimmune and related immune disorders, including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura, and autoimmune hemolytic anemia. Additionally, Edg-3 antagonists can also be used in organ transplantation. In yet another embodiment, Edg-3 agonists and antagonists can be used to treat vascular occlusive disorders. For example, activation of Edg-3 receptors by using an Edg-3 agonist will result in increased vasoconstriction which is beneficial in conditions such as migraine headaches. Inhibition of Edg-3 by an Edg3 antagonist will be beneficial in conditions such as a stroke, a subarachnoid hemorrhage, or a vasospasm such as a cerebral vasospasm. (PCT WO 01/69252 A1).

In still other aspects, the present invention provides a method of modulating an Edg-3 receptor mediated biological activity in a cell. A cell expressing the Edg-3 receptor is contacted with an amount of an Edg-3 receptor modulator sufficient to modulate the Edg-3 receptor mediated biological activity.

In yet other aspects, the present invention provides a method for modulating an Edg-3 receptor mediated biological activity in a subject. In such a method, an amount of a modulator of the Edg-3 receptor effective to modulate an Edg-3 receptor mediated biological activity is administered to the subject.

The present invention also provides compounds and compositions for use in modulating (*i.e.*, agonizing or antagonizing) Edg-3 receptor mediated biological activity or treating or preventing diseases such as those mentioned above as well as methods for synthesizing the compounds.

In certain embodiments, The Edg-3 receptor modulators are compounds of structural formula (XXXI):



(XXXI)

or a pharmaceutically available solvate or hydrate thereof, wherein:

n = 0 or 1;

o is 0, 1, 2, 3 or 4;

X is C, NR^7 O or S;

Y is C, NR^8 O or S;

R_1 is either absent or hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy,

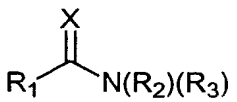
substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

R_2, R_3 and R_4 are independently hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

each R_5 is independently, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro or thio; and

$R_7$and R_8 are independently absent, hydrogen, alkyl, substituted alkyl, acyl or substituted acyl.

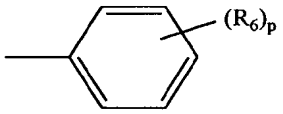
In other embodiments, Edg-3 receptor modulators are compounds of structural formula (XXXII):



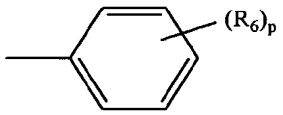
(XXXII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl,

-(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -$CO_2(CH_2)_m$(C_1-C_{10})alkyl, -$CO_2(CH_2)_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -NH(aryl), -N=C(aryl), -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

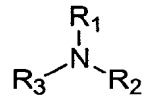
X is O, S, $C(R_5)(R_5)$ or $N(R_5)$;

R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

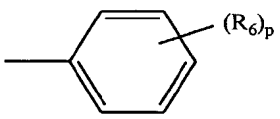
In yet other embodiments, Edg-3 receptor modulators are compounds of structural formula (XXXIII):



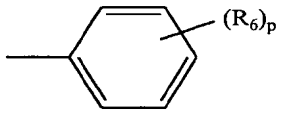
(XXXIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_m$OH, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -C(O)R_5, -C(O)NR_5R_5, -C(O)$NH(CH_2)_m(R_5)$, -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -(C_5-C_{10})heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -NHC(O)R_5, -NHC(O)OR_5, -NHC(O)NHR_5, -heterocylcoalkyl, -C(S)$N(R_5)(R_5)$, -(C_1-C_{10})alkylNHC(O)$(CH_2)_mR_5$, -(C_1-C_{10})alkylNR_5R_5, -OC(O)$(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -OC(O)OR_5, -SR_5, -S(O)R_5, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

X is O, S, or $N(R_5)$;

R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

4. BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 illustrates the selectivity of **101** for the Edg-4 receptor;

Fig. 2 illustrates a dose response curve for Edg-4 antagonists **101**, **103** and **105**;

Fig. 3 illustrates a dose response curve for **101** and LPA in HTC rat hepatoma cells transfected with human Edg-4 receptors;

Fig. 4 illustrates a dose response curve for **101** in OV202 human ovarian cancer cells;

Fig. 5 illustrates a dose response curve for **101** in CaOV-3 human ovarian cancer cells;

Fig. 6 illustrates the inhibition of VEGF production by **101** in CaOV-3 human ovarian cancer cells;

Fig. 7 illustrates the inhibition of IL-8 production by **101** in CaOV-3 human ovarian cancer cells;

Fig. 8 illustrates the inhibition of LPA-stimulated proliferation by **101** in CaOV-3 human ovarian cancer cells;

Fig. 9 illustrates the inhibition of LPA-stimulated chemotaxis by **103** in CaOV-3 human ovarian cancer cells;

Fig. 10 illustrates the lack of inhibition of S1P-stimulated migration by **103** in human umbilical vein endothelial cells;

Fig. 11 illustrates a dose response inhibition curve of LPA induced calcium mobilization by the Edg-4 antagonists **101**, **103**, **107** and **113** in HTC rat hepatoma cells transfected with human Edg-4;

Fig. 12 illustrates a dose response inhibition curve of LPA induced calcium mobilization by the Edg-4 antagonists **101**, **103**, **107** and **113** in HTC rat hepatoma cells transfected with pooled rat Edg-4 clones;

Fig. 13 illustrates a dose response inhibition curve of LPA induced calcium mobilization by the Edg-4 antagonists **101**, **103**, **107** and **113** in HTC rat hepatoma cells transfected with pooled mouse Edg-4 clones;

Figure 14 illustrates the efficacy of **101** in suppressing the tumor growth as tested by *in vivo* Z-chamber study;

Figure 15 illustrates a dose response inhibition curve of LPA induced calcium mobilization by the Edg-4 antagonist 125 in HTC cells;

Figure 16 illustrates a dose response inhibition curve of LPA induced calcium mobilization by the Edg-4 antagonist 125 in CaOV-3 cells;

Fig. 17 illustrates the selectivity of **701** for the Edg-7 receptor;

Fig. 18 illustrates the inhibition of LPA-stimulated calcium mobilization by **703** in HT-1080 human fibrosarcoma cells;

Fig. 19 illustrates the selectivity of **201** for the Edg-2 receptor;

Fig. 20 illustrates the selectivity of **203** for the Edg-2 receptor;

Fig. 21 illustrates the inhibition of LPA-stimulated calcium mobilization in immortalized ovarian surface epithelial cells by Edg-2 antagonist **203**;

Fig. 22 illustrates the effects of **203** on the inhibition of cAMP production by LPA;

Fig. 23 illustrates the inhibition of LPA-stimulated calcium mobilization in A431 human epitheloid carcinoma cells by Edg-2 antagonist **201**;

Fig. 24 illustrates the inhibition of LPA-stimulated calcium mobilization in A431 human epitheloid carcinoma cells by Edg-2 antagonists **201** and **203**, but not Edg-4 antagonist, **101**;

Figure 25 illustrates the selectivity of **301** for the Edg-3 receptor; and

Figure 26 illustrates the inhibition of S1P-stimulated calcium mobilization by **303** in mouse NIH 3T3 fibroblast cells.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1. Definitions

"Compounds of the invention" refers generally to any modulator of the LPA2 or Edg-4 receptor (e.g. human Edg-4, GenBank Accession Nos. AF23 3092 or AFO1 1466) and includes any Edg-4 receptor modulator encompassed by generic formulae disclosed herein and further includes any species within those formulae whose structure is disclosed herein. "Compounds of the invention" also refers generally to any modulator of the Edg-7 receptor (e.g. human Edg-7, GenBank Accession No. AF127138) encompassed by generic formulae disclosed herein and further includes any species within those formulae whose structure is disclosed herein. "Compounds of the invention" also refers generally to any modulator of the LPA1 or Edg-2 receptor (human Edg-2, GenBank Accession No., U78192) and includes any Edg-2 receptor modulator encompassed by generic formulae disclosed herein and further includes any species within those formulae whose structure is disclosed herein. "Compounds of the invention" also refers generally to any modulator of the S1P3 or Edg-3 receptor (e.g., human Edg-3, GenBank Accession No. X83864) and includes

any Edg-3 receptor modulator encompassed by generic formulae disclosed herein and further includes any specific Edg-3 receptor modulator within those formulae whose structure is disclosed herein. The compounds of the invention may be identified either by their chemical structure and/or chemical name. If the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the invention may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers *(i.e.,* geometric isomers), enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form *(e.g.,* geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds of the invention may also exist in several tautomeric forms including, but not limited to, the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds of the invention also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated in the compounds of the invention include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. Further, it should be understood that when partial structures of the compounds of the invention are illustrated, brackets indicate the point of attachment of the partial structure to the rest of the compound.

"Composition of the invention" refers to at least one compound of the invention and a pharmaceutically acceptable vehicle, with which the compound is administered to a patient. When administered to a patient, the compounds of the invention are administered in isolated form, which means separated from a synthetic organic reaction mixture.

"Alkyl" refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include,

but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

The term "alkyl" is specifically intended to include groups having any degree or level of saturation, *i.e.,* groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions "alkanyl," "alkenyl," and "alkynyl" are used. Preferably, an alkyl group comprises from 1 to 20 carbon atoms.

"Alkanyl" refers to a saturated branched, straight-chain or cyclic alkyl group derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl *(sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), cyclobutan-1-yi, *etc.*; and the like.

"Alkenyl" refers to an unsaturated branched, straight-chain or cyclic alkyl group having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

"Alkynyl" refers to an unsaturated branched, straight-chain or cyclic alkyl group having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-l-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

"Acyl" refers to a radical -C(O)R, where R is hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl as defined herein. Representative examples include, but are not limited to formyl, acetyl, cylcohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl and the like.

"Acylamino" refers to a radical -NR'C(O)R, where R' and R are each independently hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, as defined herein. Representative examples include, but are not limited to, formylamino, acetylamino, cylcohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino, benzylcarbonylamino and the like.

"Alkylamino" means a radical -NHR where R represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methylamino, ethylamino, 1-methylethylamino, cyclohexyl amino and the like.

"Alkoxy" refers to a radical -OR where R represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, cyclohexyloxy and the like.

"Alkoxycarbonyl" refers to a radical -C(O)-alkoxy where alkoxy is as defined herein.

"Alkylarylamino" refers to a radical -NRR' where R represents an alkyl or cycloalkyl group and R' is an aryl as defined herein

"Alkylsulfonyl" refers to a radical -$S(O)_2R$ where R is an alkyl or cycloalkyl

group as defined herein. Representative examples include, but are not limited to methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl and the like.

"Alkylsulfinyl" refers to a radical -S(O)R where R is an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl and the like.

"Alkylthio" refers to a radical -SR where R is an alkyl or cycloalkyl group as defined herein that may be optionally substituted as defined herein. Representative examples include, but are not limited to methylthio, ethylthio, propylthio, butylthio, and the like.

"Amino" refers to the radical $-NH_2$.

"Aryl" refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Preferably, an aryl group comprises from 6 to 20 carbon atoms.

"Arylalkyl" refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. Preferably, an arylalkyl group is (C_6-C_{30}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_{10}) and the aryl moiety is (C_6-C_{20}).

"Arylalkyloxy" refers to an -O-arylalkyl radical where arylalkyl is as defined herein.

"Arylamino" means a radical -NHR where R represents an aryl group as defined herein.

"Aryloxycarbonyl" refers to a radical -C(O)-O-aryl where aryl is as defined herein.

"Azido" refers to the radical $-N_3$.

"Carbamoyl" refers to the radical $-C(O)N(R)_2$ where each R group is independently hydrogen, alkyl, cycloalkyl or aryl as defined herein, which may be optionally substituted as defined herein.

"Carboxy" means the radical -C(O)OH.

"Cyanato" means the radical -OCN.

"Cyano" means the radical -CN.

"Cycloalkyl" refers to a saturated or unsaturated cyclic alkyl group. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. In a preferred embodiment, the cycloalkyl group is (C_3-C_{10}) cycloalkyl, more preferably (C_3-C_6) cycloalkyl.

"Cycloheteroalkyl" refers to a saturated or unsaturated cyclic alkyl group in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, *etc.* Where a specific level of saturation is intended, the nomenclature "cycloheteroalkanyl" or

"cycloheteroalkenyl" is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from dioxanes, dioxolanes, epoxides, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran and the like.

"Cycloheteroalkyloxycarbonyl" refers to a radical -C(O)-OR where R is cycloheteroalkyl is as defined herein.

"Dialkylamino" means a radical -NRR' where R and R' independently represent an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to dimethylamino, methylethylamino, di-(1-methylethyl)amino, (cyclohexyl)(methyl)amino, (cyclohexyl)(ethyl)amino, (cyciohexyl)(propyl)amino, and the like.

"Halo" means fluoro, chloro, bromo, or iodo.

"Haloalkyl" means an alkyl radical substituted by one or more halo atoms wherein alkyl and halo is as defined herein.

"Heteroalkyloxy" means an -O-heteroalkyl group where heteroalkyl is as defined herein.

"Heteroalkyl, Heteroalkanyl, Heteroalkenyl, Heteroalkynyl" refer to alkyl, alkanyl, alkenyl and alkynyl groups, respectively, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic groups. Typical heteroatomic groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, -NR'-, =N-N=, -NN-, -N=N-NR-, -PH-,$-P(O)_2-$, $-O-P(O)_2-$, -S(O)-, $-S(O)_2-$, $-SnH_2-$ and the like, wherein R' is hydrogen, alkyl, substituted alkyl, cycloallcyl, substituted cycloalkyl, aryl or substituted aryl.

"Heteroaryl" refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan,

imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoiine, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Preferably, the heteroaryl group is between 5-20 membered heteroaryl, with 5-10 membered heteroaryl being particularly preferred. Preferred heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

"Heteroaryloxy" refers to an -O-heteroarylalkyl radical where heteroarylalkyl is as defined herein.

"Heteroaryloxycarbonyl" refers to a radical -C(O)-OR where R is heteroaryl as defined herein.

"Heteroarylalkyl" refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylalkenyl and/or heterorylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-30 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is 1-10 membered and the heteroaryl moiety is a 5-20 membered heteroaryl.

"Hydroxy" refers to the radical -OH.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkoxycarbonyl *(e.g.,* acetoxy), aryloxycarbonyl, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy *(e.g,* 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

"Nitro" refers to the radical $-NO_2$.

"Oxo" refers to the divalent radical =O.

"Pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

"Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chiorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

"Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

"Patient" includes humans. The terms "human" and "patient" are used interchangeably herein.

"Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder *(i.e.,* causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease).

"Prodrug" refers to a pharmacologically inactive derivative of a drug molecule that requires a transformation within the body to release the active drug. Typically, prodrugs are designed to overcome pharmaceutical and/or pharmacokinetically based problems associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug.

"Promoiety" refers to a form of protecting group that when used to mask a functional group within a drug molecule converts the drug into a prodrug. Typically, the promoiety will be attached to the drug *via* bond(s) that are cleaved by enzymatic or non-enzymatic means *in vivo.* Ideally, the promoiety is rapidly cleared from the body upon cleavage from the prodrug.

"Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in Green *et al,* "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991) and Harrison *et al.,* "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

"Substituted" refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, -X, -R_{14}, -OS, =O, -OR_{14}, -SR_{14}, S^-, =S -NR_{14}, R_{15},

$=NR_{14}$,$-CX_3$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2O^-$, $-S(O)_2OH$, $-S(O)_2R_{14}$, $-OS(O_2)O^-$, $-OS(O)_2R_{14}$, $-P(O)(O)_2$, $-P(O)(OR_{14})(O)$, $-OP(O)(0R_{14})(OR_{15})$, $-C(O)R_{14}$, $-C(S)R_{14}$, $-C(O)0R_{14}$, $-C(O)NR_{14}R_{15}$, $-C(O)O^-$, $-C(S)OR_{14}$, $-NR_{16}C(O)NR_{14}R_{15}$, $-NR_{16}C(S)NR_{14}R_{15}$, $NR_{17}C(NR_{16})NR_{14}R_{15}$ and $-C(NR_{16})NR_{14}R_{15}$, where each X is independently a halogen; each R_{14}, R_{15}, R_{16} and R_{17} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted alkyl, arylalkyl, substituted alkyl, cycloalkyl, substituted alkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR_{15}R_{19}$, $-C(O)R_{15}$ or $-S(O)_2R_{15}$ or optionally R_{15} and R_{19} together with the atom to which they are both attached form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and R_{15} and R_{19} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted alkyl, arylalkyl, substituted alkyl, cycloalkyl, substituted alkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroallcyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

"Sulfonylamino" refers to a radical $-NR'S(O_2)R$, where R' and R are each independently hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, as defined herein.

"Therapeutically effective amount" means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the patient to be treated.

"Thio" refers to the radical -SH.

"Thiocyanato" refers to the radical -SCN.

"Thiono" refers to the divalent radical =S.

"Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder *(i.e.,* arresting or reducing the

development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, *(e.g.,* stabilization of a discernible symptom), physiologically, *(e.g.,* stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

Reference will now be made in detail to preferred embodiments of the invention. While the invention will be described in conjunction with the preferred embodiments, it will be understood that it is not intended to limit the invention to those preferred embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

5.2. The Use of the Edg-4 Compounds of the Invention

The present invention provides a method of modulating an LPA2 or Edg-4 receptor *(e.g.,* human Edg-4, GenBank Accession Nos. AF233092 or AF011466) mediated biological activity. A cell expressing the Edg-4 receptor is contacted with an amount of an Edg-4 receptor agonist or antagonist sufficient to modulate the Edg-4 receptor mediated biological activity.

Those of skill in the art will appreciate that Edg-4 is a G protein coupled receptor ("GPCR"). The Edg-4 (LPA2) receptor is encoded by an endothelial differentiation gene and along with related receptors, Edg-2 (LPA1) and Edg-7 (LPA3), binds lysophosphatidic acid ("LPA"). Preferably, the Edg-4 receptor is a human receptor.

The Edg-4 receptor may be expressed by recombinant DNA methods well known to those of skill in the art. Particularly useful cell types for expressing and assaying Edg-4 include, but are not limited to, HTC4 (rat hepatoma cells), RH7777 (rat hepatoma cells), HepG2 (human hepatoma cells), CHO (Chinese hamster ovary cells) and HEK-293 (human embryonic kidney cells). Particularly useful vectors for expressing G-protein receptors include, but are not limited to, pLXSN and pCMV (Clontech Labs, Palo Alto, CA; Invitrogen Corporation, Carlsbad, CA).

DNA encoding Edg-4 is well known *(e.g.* human Edg-4, GenBank Accession Nos. AF233092 or AF011466) and can be transfected into human or mammalian cells

according to methods known to those of skill in the art. For example, DNA encoding human Edg-4 can be co-transfected with a standard packaging vector, such as those described above, which provides an ecotropic envelope for viral replication, into a packaging cell line such as GP-293 (Clontech Labs, Palo Alto, CA).

Alternatively, DNA encoding Edg-4 can be transfected into the EcoPack-293 cell line which has, in addition to *gag and pol,* the *env* gene to produce an ecotropic envelope. Both methods *(i.e.,* co-transfection with a packaging vector or use of EcoPack-293) enable the production of an ecotropic envelope for viral packaging, and can thus advantageously be used to transfect rat and mouse cells. For use in human and other mammalian cells, AmphoPack-293 cell line can be used (Clontech Labs, Palo Alto, CA).

In addition, a number of natural cell lines naturally express Edg-4 receptors. These include, but are not limited to, CaOV-3 human ovarian cancer cells, MDA-MB-453 and MDA-MB-231 breast cancer cells, HT-1080 human fibrosarcoma, HUVEC cells and OV202 human ovarian cancer cells (ATCC, Manassas, VA; Vec Technologies Inc. (Rensselaer, NY); Dr. Edward Goetzl, University of California, San Francisco, San Francisco, CA).

Those of skill in the art will appreciate that cells which express the Edg-4 receptor may grown *in vitro* or may be part of a complex organism such as, for example, a mammal. It is contemplated that the methods of the current invention will be applicable to modulation of Edg-4 receptor activity, regardless of the local environment. In one preferred embodiment, cells that express the Edg-4 receptor are grown *in vitro (i.e.,* are cultured). In another preferred embodiment, cells that express the Edg-4 receptor are *in vivo (i.e.,* are part of a complex organism).

The cells, in which the method of the invention may be practiced include, but are not limited to, hepatoma cells, ovarian cells, epithelial cells, fibroblast cells, neuronal cells, cardiac myocytes, endothelial cells, carcinoma cells, pheochromocytoma cells, myoblast cells, platelet cells and fibrosarcoma cells. More specifically, the cells in which the invention may be practiced include, but are not limited to, 0V202 human ovarian cells, HTC rat hepatoma cells, CAOV-3 human ovarian cancer cells, MDA-MB-453 breast cancer cells, MDA-MB-231 breast cancer cells, HUVEC, A431 human epitheloid carcinoma cells and HT-1080 human fibrosarcoma cells.

In another aspect, an Edg-4 receptor mediated biological activity is modulated

in a subject or in an animal model. A therapeutically effective amount of a modulator of the Edg-4 receptor is administered to the subject or an animal. Preferably, the subject or animal is in need of such treatment.

The biological activity mediated by the Edg-4 receptor may include, for example, calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP formation or actin polymerization. Preferably, the biological activity mediated by the Edg-4 receptor includes, but is not limited to, apoptosis, angiogenesis, inhibition of wound healing, inflammation, cancer invasiveness or atherogenesis. Most preferably, the biological activity mediated by the Edg-4 receptor is cell proliferation, which may lead to ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colon cancer or prostrate cancer. In one embodiment, cell proliferation is stimulated by LPA.

In another embodiment, the biological activity mediated by the Edg-4 receptor may include increasing fatty acids levels *(e.g.,* free fatty acids and lyso-phosphatidylcholine) which may lead to acute lung diseases, such as adult respiratory distress syndrome ("ARDS") and acute inflammatory exacerbation of chronic lung diseases like asthma.

In yet another embodiment, compounds that block Edg-4 can be potentially effective immunosuppressive agents because activated T cells have Edg-4 receptors (Zheng *et al.,* **2000**, *FASEB J* 14:2387-2389). Edg-4 antagonists may be useful in a variety of autoimmune and related immune disorders, including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura, and autoimmune hemolytic anemia. Additionally, Edg-4 antagonists can be used in organ transplantation.

In one embodiment, the modulator exhibits selectivity for the Edg-4 receptor. For example, the modulator exhibits at least about 5 to about 200 fold inhibitory selectivity for Edg-4 relative to other Edg receptors. Inhibitory selectivity, can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.25 (Example 25), 6.27 (Example 27) and 6.28 (Example 28) respectively. In a preferred embodiment, inhibitory selectivity can be measured by a calcium mobilization assay.

Other assays suitable for determining inhibitory selectivity would be known to one of skill in the art.

In some embodiments, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to other non-Edg receptors, including, but not limited to, other GPCRs, ion channels, growth factor receptors and the like.

In other embodiments, the modulator exhibits at least about 63 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 30 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In one embodiment, the modulator exhibits at least about 5 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In yet another embodiment, the modulator exhibits at least about 63 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In another embodiment, the modulator exhibits at least about 30 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 5 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In a preferred embodiment, the modulator of cell proliferation exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In another embodiment, the modulator exhibits activating selectivity for the Edg-4 receptor. For example, the modulator exhibits at least about 5 to about 200 fold activating selectivity for Edg-4 relative to other Edg receptors. Activating selectivity,

can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.13 (Example 13), 6.15 (Example 15) and 6.16 (Example 16) respectively. In a preferred embodiment, activating selectivity can be measured by a calcium mobilization assay. Other assays suitable for determining activating selectivity would be known to one of skill in the art.

In one embodiment, the modulator exhibits at least about 200 fold activating selectivity for Edg-4 relative to other non-Edg receptors, including, but not limited to, other GPCRs, ion channels, growth factor receptors and the like.

In another embodiment, the modulator exhibits at least about 63 fold activating selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 30 fold activating selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 10 fold activating selectivity for Edg-4 relative to other Edg receptors.

In one embodiment, the agonist modulator exhibits at least about 5 fold activating selectivity for Edg-4 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 200 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In yet another embodiment, the modulator exhibits at least about 63 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In another embodiment, the modulator exhibits at least about 30 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 10 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about *5* fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In a preferred embodiment, of cell proliferation exhibits at least about 200 fold activating selectivity for Edg-4 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 10 fold activating selectivity for Edg-4 relative to other Edg receptors.

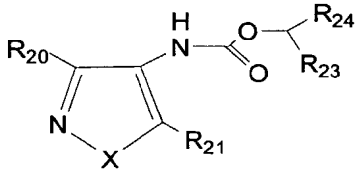
In still another embodiment, the modulator of cell proliferation exhibits at least about 10 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least

about 200 fold activating selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

In one embodiment, the Edg-4 modulator is not a lipid. In another embodiment, the modulator of Edg-4 receptor mediated biological activity does not contain a phosphate group such as a phosphoric acid, a cyclic phosphate ester or a linear phosphate ester. In another embodiment, the modulator of the Edg-4 receptor is not a phospholipid. The term "phospholipid" includes all phosphate (both phosphate esters and phosphoric acids) containing glycerol derivatives with an alkyl chain of greater 10 carbon atoms or greater, any N-acyl ethanolamide phosphate derivative (both phosphate esters and phosphoric acids), LPA, S1P or any of their analogues (both phosphate esters and phosphoric acids) (see, *e.g.*, Bandoh, *et al,* **2000**, *FEBS Lett.* 428, *759*; Bittman *et al.*, **1996**, *J. Lipid Research* 391; Lilliom *et al,* **1996**, *Molecular Pharmacology* 616, Hooks *et al,* **1998**, *Molecular Pharmacology* 188; Fischer *et al,* **1998**, *Molecular Pharmacology* 979; Heise *et al,* **2001**, *Molecular Pharmacology* 1173; Hopper *et al.*, **1999**, *J. Med. Chem.* 42 (6):963-970; Tigyi *et al,* **2001**, *Molecular Pharmacology 1161).*

In another embodiment, the modulator is also not a compound of structural formula:



or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

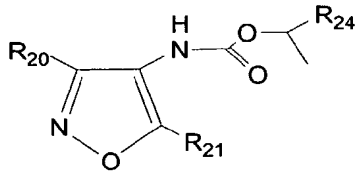
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

or alternatively R_{23} and R_{24} form a cycloalkyl ring (International Application No: WO 01/60819).

In another embodiment, the modulator is not any compound of the formula below:



wherein R_{20}, R_{21} and R_{24} are as previously defined. In yet another embodiment the modulator is not any compound disclosed in International Application No: WO 01/60819.

The Edg-4 modulator may be a biomolecule such as a nucleic acid, protein, *(i.e.,* an enzyme or an antibody) or oligosaccharide or any combination thereof. Alternatively, the Edg-4 modulator may be oligomers or monomers of the above biomolecules such as amino acids, peptides, monosaccharides, disaccharides, nucleic acid monomers, dimers, *etc.,* or any combination thereof. The Edg-4 modulator may also be a synthetic polymer or any combination of synthetic polymer with biomolecules including monomers or oligomers of biomolecules.

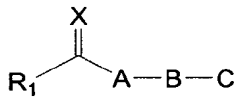
The Edg-4 modulator may also be an organic molecule of molecular weight less than 750 daltons. In one embodiment, the molecular weight is about 200 to about 1000 daltons. In another embodiment, the molecular weight is about 200 to about 750 daltons. In yet another embodiment, the molecular weight is about 200 to about 500 daltons. Preferably, the molecular weight is about 300 to about 500 daltons.

Without wishing to be bound by any particular theory or understanding, the modulator may, for example, facilitate inhibition of the Edg-4 receptor through direct binding to the LPA binding site of the receptor, binding at some other site of the Edg-4 receptor, interference with Edg-4 or LPA biosynthesis, covalent modification of either LPA or the Edg-4 receptor, or may otherwise interfere with Edg-4 mediated signal transduction.

In one embodiment, the agonist or antagonist binds to the Edg-4 receptor with a binding constant between about 10 μM and about 1 fM. In another embodiment, the modulator binds to the Edg-4 receptor with a binding constant between about 10 μM

and about 1 nM. In another embodiment, the modulator binds to the Edg-4 receptor with a binding constant between about 1 μM and about 1 nM. In another embodiment, the modulator binds to the Edg-4 receptor with a binding constant between about 100 nM and about 1 nM. In another embodiment, the modulator binds to the Edg-4 receptor with a binding constant between about 10 nM and about 1 nM. Preferably, the modulator binds to the Edg-4 receptor with a binding constant better *(i.e.,* less) than about 10 nM.

In a specific embodiment, the modulator is a compound of structural formula (I):



(I)

or a pharmaceutically available solvate or hydrate thereof, wherein:

R_1 is hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkylarylamino, substituted alkylarylamino, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylamino, substituted arylamino, arylalkyl, substituted arylalkyl, dialkylamino, substituted dialkylamino, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl sulfonylamino or substituted sulfonylamino;

X=O or S;

A is NR_2, O or 5;

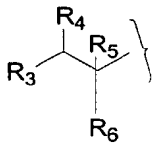
R_2 is hydrogen, alkyl or substituted alkyl; and

B and C are independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or

substituted cycloheteroalkyl.

Preferably, R_1 is alkyl, substituted alkyl, substituted aryl, substituted aryl, arylalkyloxy or substituted sulfonylamino. More preferably, R_1 is substituted alkyl. Even more preferably, R_1 is substituted haloalkyl. Most preferably, R_1 is substituted trifluoroalkyl (preferably, trifluoroalkanyl).

In a preferred embodiment, R_1 has the structural formula (II):



(II)

wherein:

R_3 is haloalkyl or substituted haloalkyl;

R_4 is oxo or thiono; and

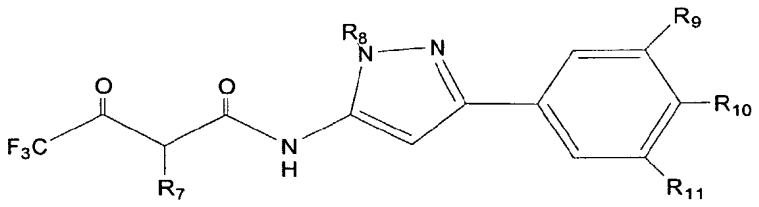
R_5 and R_6 are independently hydrogen, halo, alkyl or substituted alkyl.

Preferably, R_3 is fluoroalkyl, R_4 is oxo and R_5 and R_6 are independently hydrogen, halo or alkyl. More preferably, R_3 is trifluoromethyl, R_4 is oxo and R_5 and R_6 are independently hydrogen, chloro or methyl.

In one preferred embodiment, R_5 and R_6 are hydrogen. In another preferred embodiment, R_5 is hydrogen and R_6 is chloro or methyl.

Preferably in any of the above embodiment, X is O, A is NR_2 and R_2 is hydrogen. In another preferable version of the above embodiments, B and C are alkyl, substituted alkyl, independently, aryl, substituted aryl, heteroaryl or substituted heteroaryl. More preferably, B and C are independently indolo, substituted indolo, imidazolo, substituted, imidazolo, pyrazolo, substituted pyrazolo, phenyl or substituted phenyl. Even more preferably, B is heteroaryl or substituted heteroaryl and C is aryl or substituted aryl. Most preferably, B is pyrazolo or substituted pyrazolo and C is phenyl or substituted phenyl.

In a more specific embodiment, the modulator is a compound of structural formula (III):



(III)

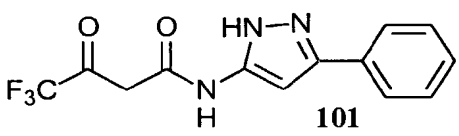
wherein:

R_7 is hydrogen, alkyl, substituted alkyl or halo;

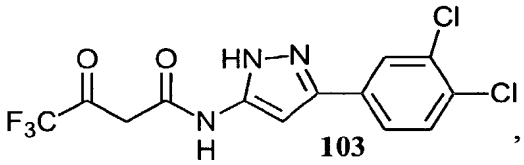
R_8 is hydrogen, carbamoyl or substituted carbamoyl; and

R_9, R_{10} and R_{11} are independently hydrogen, alkoxy, substituted alkoxy, halo or optionally, R_9 and R_{10} together with the carbons to which they are attached form a [1,3] dioxolane ring.

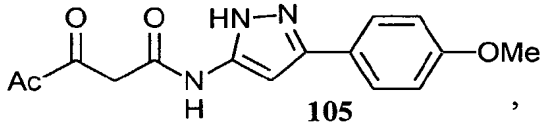
Preferred modulators include compounds of the structural formula shown below:



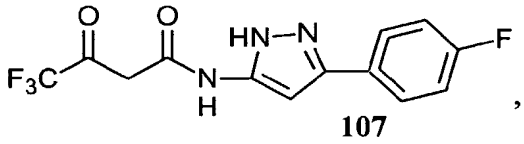
101 ,



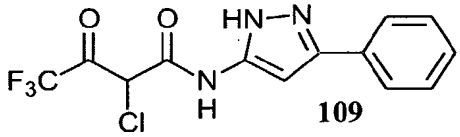
103 ,



105 ,



107 ,



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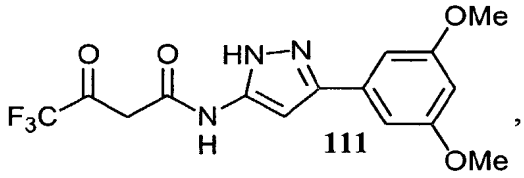
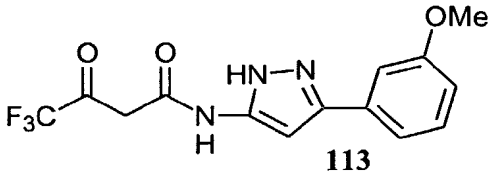
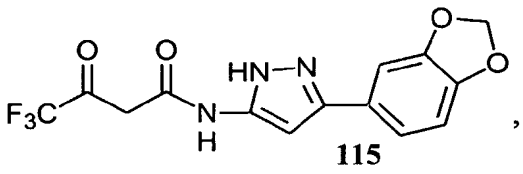


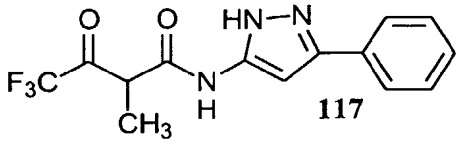
111 ,



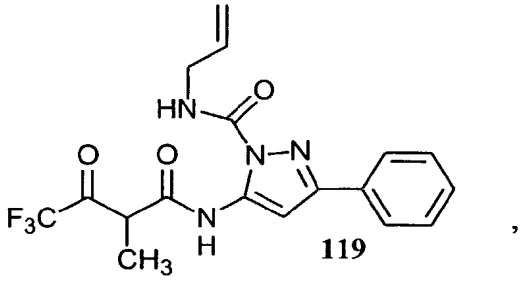
113 ,



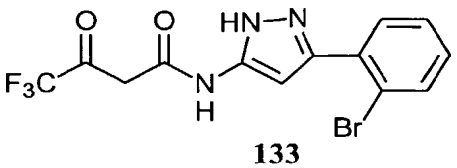
115 ,



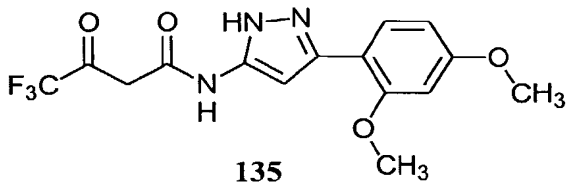
117 ,



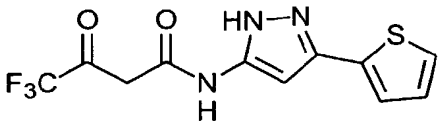
119 ,



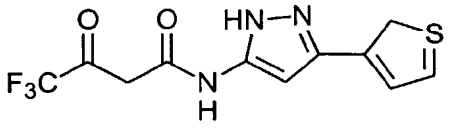
133 ,



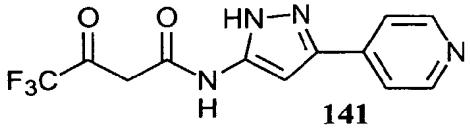
135 ,



137 ,

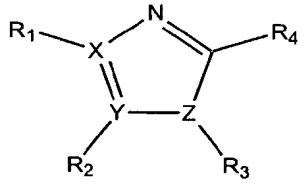


139 or



141 .

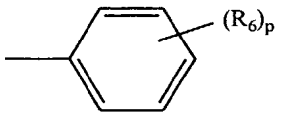
In another embodiment, the agonists or antagonists that can be utilized as part of the methods of the present invention are compounds of structural formula (IV):



(IV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, $-(C_5\text{-}C_{10})$cycloheteroaryl, $-(C_3\text{-}C_6)$cycloheteroalkyl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-NR_5R_5$, $=NR_5$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_3\text{-}C_{10})$cycloheteroalkyl$(R_5)_m$, $-(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X and Y are each independently C or N; and

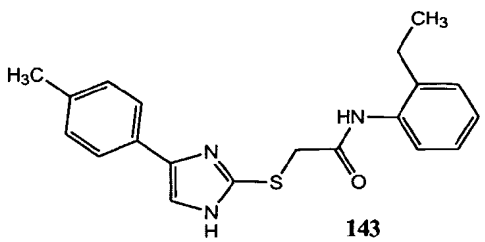
Z is O, S, C or N, wherein if Z is O or S, then R_3 is an electron pair;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_3 and R_4 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

Some illustrative examples of the modulators of this embodiment include:



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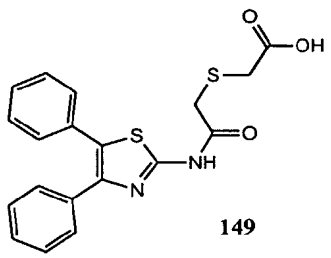

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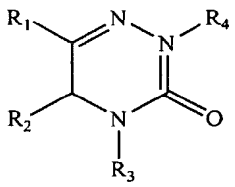
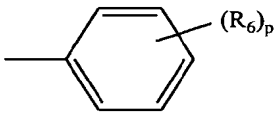
Another embodiment of the present invention is directed to compounds of structural formula (V), which can be utilized for the purpose of this invention:



(V)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), $-CO_2(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1\text{-}C_{10})$alkyl, $-NHC(O)NH(C_1\text{-}C_{10})$alkyl, $-OC(O)(C_1\text{-}C_{10})$alkyl, $-OC(O)O(C_1\text{-}C_{10})$alkyl, or $-SO_2NH_2$;

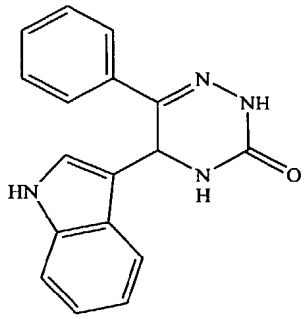
m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5; and

R_1 and R_2 or R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In a specific embodiment, R_1 and R_2 are independently aryl, substituted aryl, heteroaryl or substituted heteroaryl. In a more specific embodiment, R_2 is indole, and R_3 and R_4 are hydrogen.

Illustrative examples of the modulators of this embodiment include:



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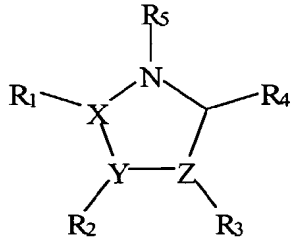
and its (+) and (-) enantiomers.

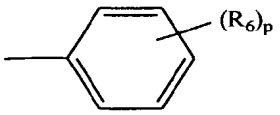
In another embodiment, the modulator is a compound of structural formula (VI):



(VI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})alkyl(C_1\text{-}C_{10})alkyl$, $-O(C_1\text{-}C_{10})alkyl$, $-C(O)(C_1\text{-}C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})alkyl(C_1\text{-}C_{10})alkyl)$, $-CO_2(C_1\text{-}C_{10})alkyl$, $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3\text{-}C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1\text{-}C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1\text{-}C_{10})alkyl$, $-NHC(O)NH(C_1\text{-}C_{10})alkyl$, $-OC(O)(C_1\text{-}C_{10})alkyl$, $-OC(O)O(C_1\text{-}C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X, Y and Z are independently O, S, C or N, wherein if X, Y or Z is O or S, R_1 is an electron pair;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;

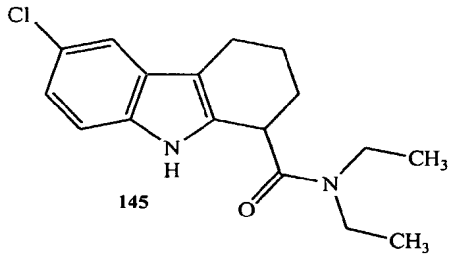
R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_1 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_4 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In a specific embodiment, R_1 and R_2 together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring. In a more specific embodiment, R_1 and R_2 together, and R_3 and R_4 together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring. In an even more specific embodiment, R_1 and R_2 together, and R_3 and R_4 together form a 6-membered substituted or unsubstituted cyclic or aromatic ring. Even more specifically, R_1 and R_2, and R_3 and R_4 form a 6-membered substituted aromatic or cyclic ring.

Illustrative modulators of the invention include, but are not limited to, the following compound:



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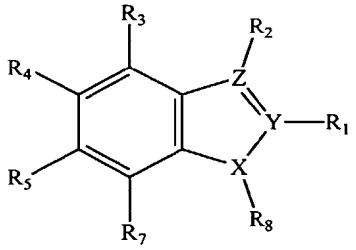
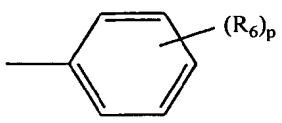
In a specific embodiment, the modulator is a compound of structural formula (VII):



(VII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$,

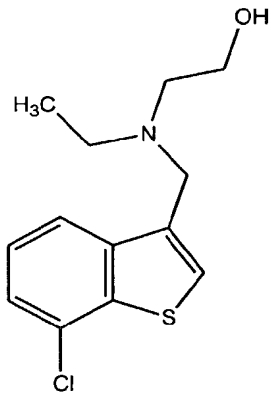
-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

m is independently an integer ranging from 0 to 8;

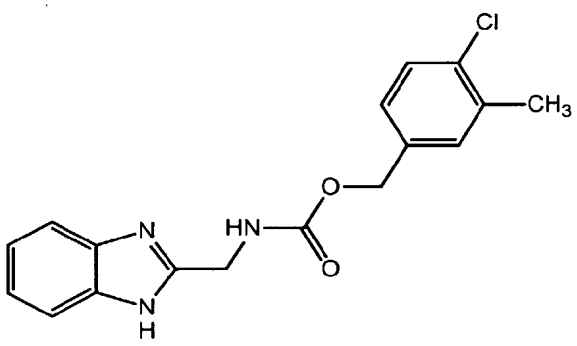
p is independently an integer ranging from 0 to 5;

X is O, S, C or N, wherein if X is O or S, R_1 is an electron pair; and

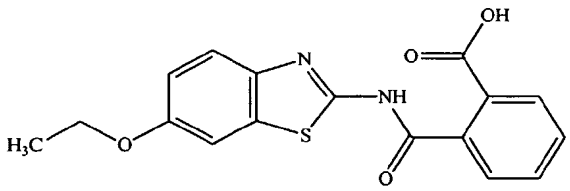
Y and Z are independently N or C, wherein if Y or Z is N, R_1 and R_2 are each an electron pair. Illustrative modulators of the invention include:



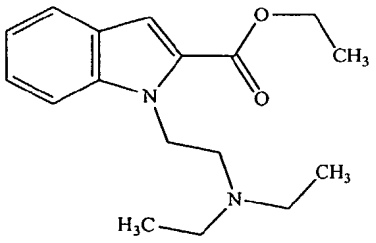
147 ,



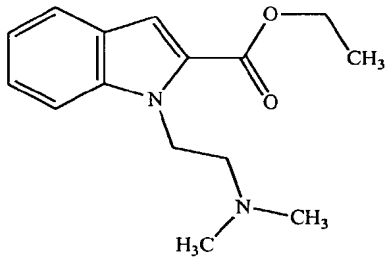
155



157 ,

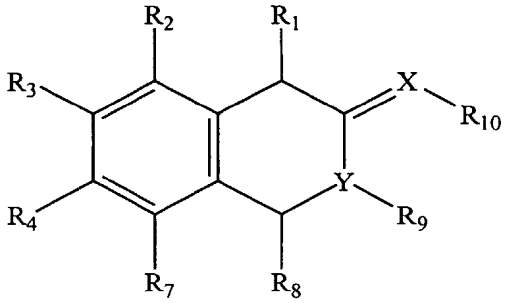


165 ,



167 .

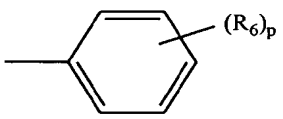
In another specific embodiment, the modulator is a compound of structural formula (VIII):



(VIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

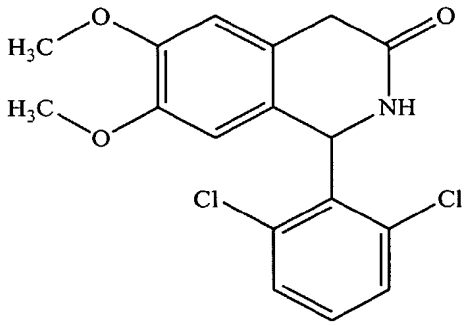
each R_6 is independently -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5; and

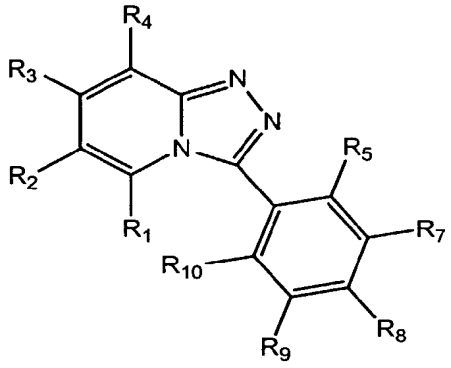
X and Y are independently O, S or N, wherein if X or Y is O or S, R_9 and R_{10} are an electron pair.

In another embodiment, R_7 is a substituted or unsubstituted aryl. An illustrative example of these Egd-4 modulators includes:



125

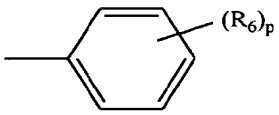
In another embodiment, the modulator is a compound of structural formula (IX)



(IX)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



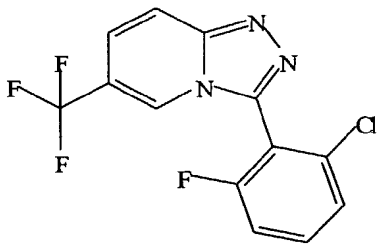
wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

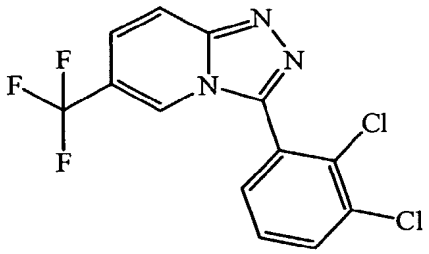
m is independently an integer ranging from 0 to 8; and

p is independently an integer ranging from 0 to 5.

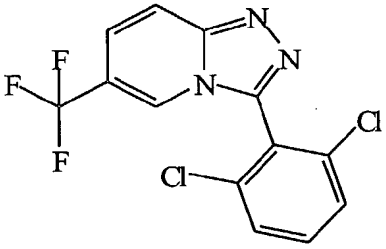
In a specific embodiment, R_2 is a substituted alkyl, and one or more of R_5, R_7, R_8, R_9 and R_{10} are halos. In a more specific embodiment, R_2 is a halo-substituted alkyl. In an even more specific embodiment, R_2 is CF_3. Specific examples of the modulators include:



127

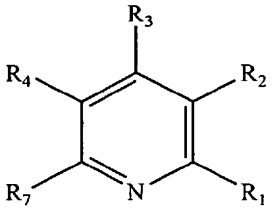


129



131

In another specific embodiment, the modulator is a compound of structural formula (X):

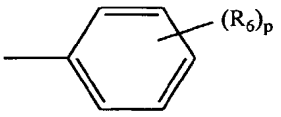


(X)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$,

$-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-CO_2H$, $-(C_1-C_{10})alkylC(O)NH(CH_2)_mR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

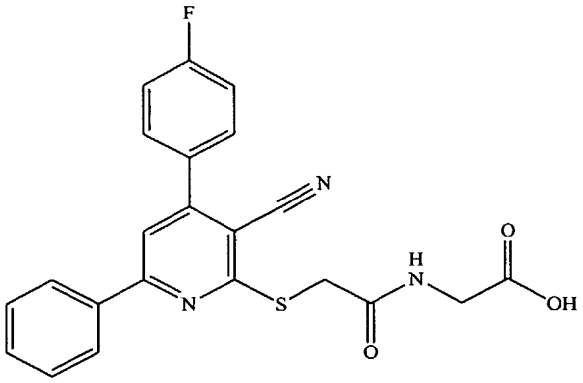
R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In a specific embodiment, R_3 and R_7 are substituted or unsubstituted aryls. An illustrative modulator of the invention includes:



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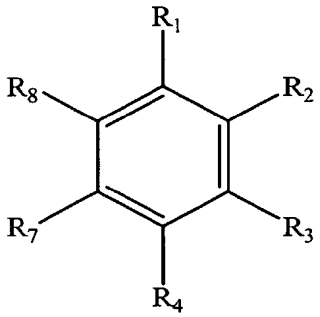
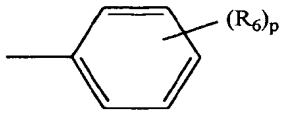
In yet another specific embodiment, the modulator is a compound of structural formula (XI):



(XI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, $-(C_5\text{-}C_{10})$cycloheteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

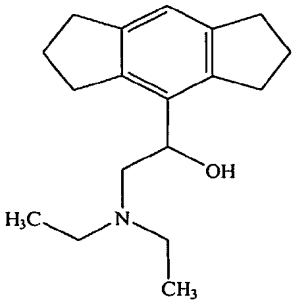
R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_7 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In another embodiment, R_2 and R_3 together form a 5-membered ring. In a more specific embodiment, R_2 and R_3 together, and R_7 and R_8 together form a 5-membered ring. Illustrative examples of the modulators of the invention include:



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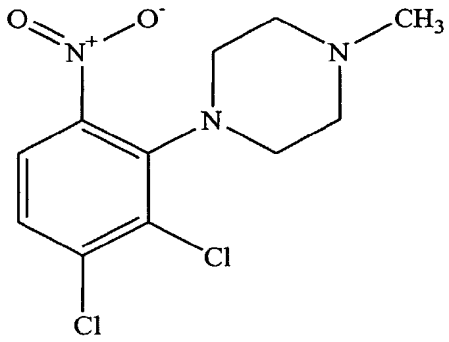
Another illustrative compound of the invention has the following structure:



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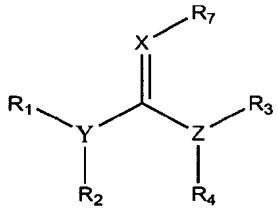
In another specific embodiment, the modulator is a compound of structural formula (XII):

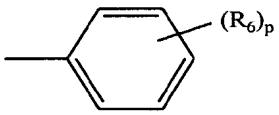


(XII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$(CH_2)_mN(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -$C(OH)R_5$, -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl,

-(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -(C_5-C_{10})heteroaryl, -(C_5-C_{10})cycloheteroaryl, -(C_3-C_6)cycloheteroalkyl, -naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_mR_5$, -NHC(O)R_5, -NHC(O)OR_5, -NHC(O)NHR_5, $-NR_5R_5$, $=NR_5$, -(C_1-C_{10})alkylNHC(O)$(CH_2)_mR_5$, -(C_3-C_{10})cycloheteroalkyl$(R_5)_m$, $-(CH_2)_mR_5$, -(C_1-C_{10})alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, -OC(O)OR_5, $-SR_5$, -S(O)R_5, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, $-C(O)NH(CH_2)_m$(C_1-C_{10})alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH$((C_1-C_{10})alkyl(C_1-C_{10})alkyl), $-CO_2$(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_m$(C_1-C_{10})alkyl, $-CO_2(CH_2)_mH$, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

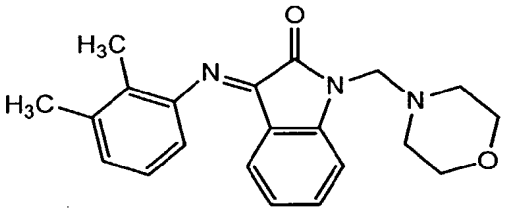
p is independently an integer ranging from 0 to 5;

R_3 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring.

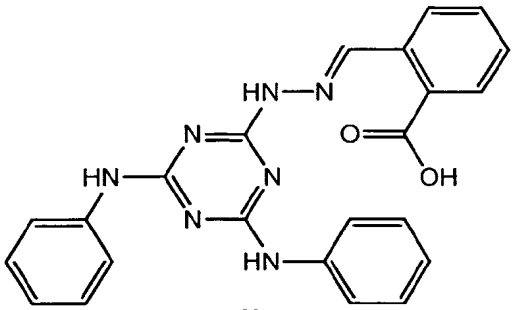
R_1 or R_2 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring;

R_2 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring.

Illustrative examples of the modulators of the invention include:



159



163

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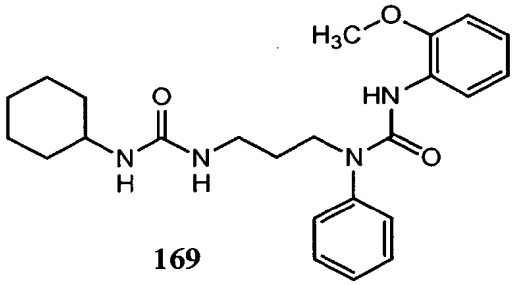

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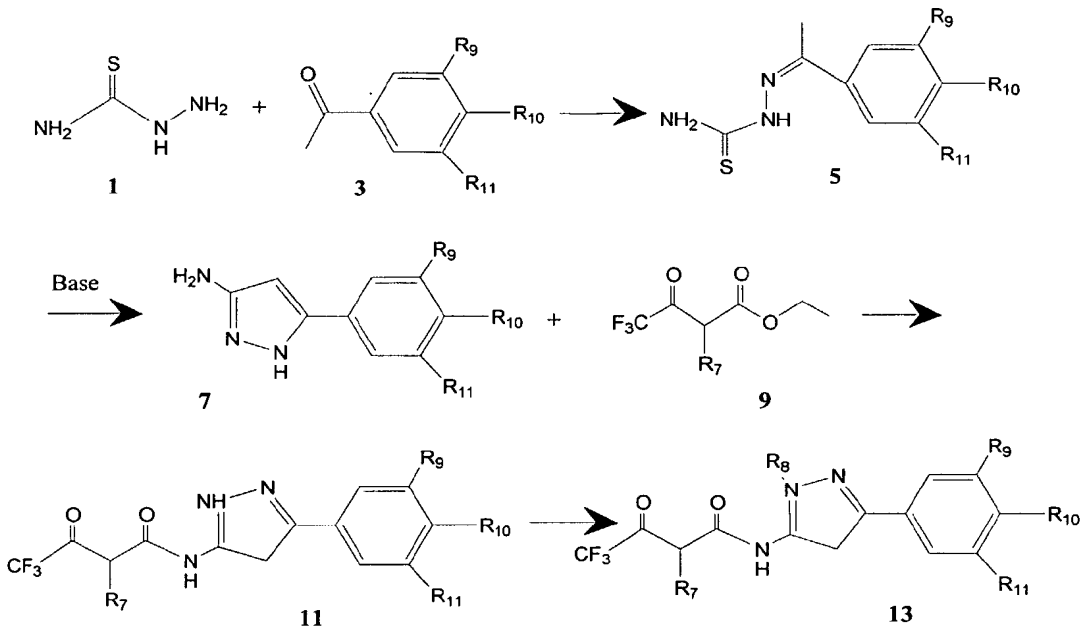
5.3. Synthesis of the Edg-4 Compounds of the Invention

Certain compounds of the invention may be obtained *via* the synthetic methods illustrated in Schemes 1 and 2. Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods. Other methods for synthesis of the compounds described herein are either described in the art or will he readily apparent to the skilled artisan in view of general references well-known in the art (See *e.g.*, Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991); Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-17, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for

Organic Synthesis," John Wiley & Sons, 1995) and may be used to synthesize the compounds of the invention. Accordingly, the methods presented in Schemes 1 and 2 herein are illustrative rather than comprehensive.

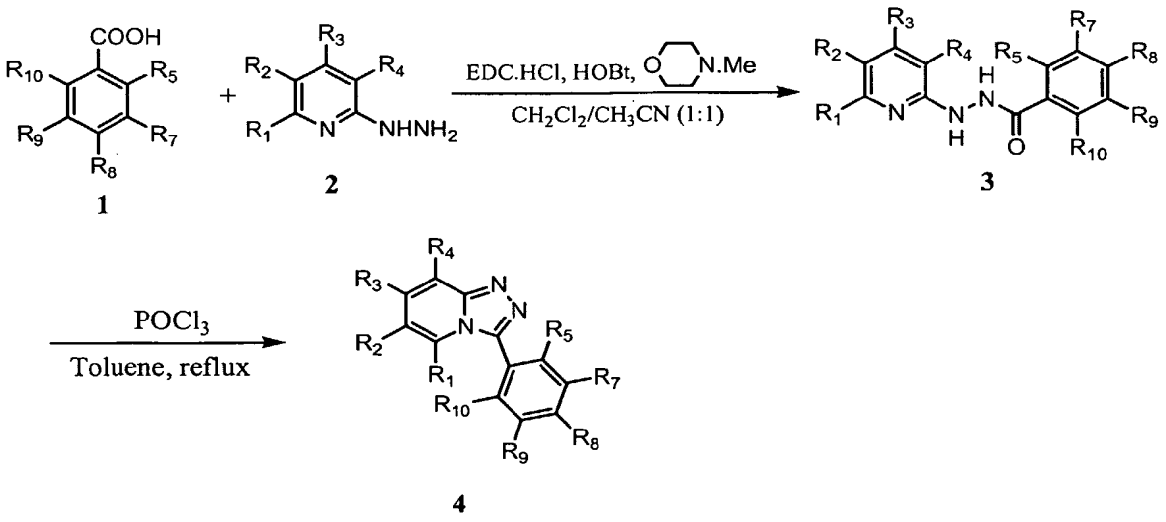
Scheme 1



The compounds depicted in Scheme 1 are compounds of structural formula (I). Generally, compounds of structural formula (I) may be made by the route depicted in Scheme 1. Condensation of commercially available thiosemicarbazide 1 with acetophenone **3** in the presence of acid, *(e.g.,* acetic acid) provides thiosemicarbazone **5**. In the presence of strong base, *(e.g.,* lithium diisopropylamide) ring formation takes place to form amine **7**. Condensation of amine **7** with acetoacetate **9** provides the butyramide **11**, which may be alkylated or acylated with an activated urea derivative to provide butyramide **13** (R_8 = alkyl, or -C(0)NHR_{20}, where R_{20} is alkyl).

Those of skill in the art will appreciate that a wide variety of esters other than the acetoacetate **9** depicted may be condensed with amine **7** to provide compounds of the invention. Further the skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (I) other than those depicted above.

Scheme 2



The compounds depicted in Scheme 2 are compounds of structural formula (IX). Generally, compounds of structural formula (IX) may be made by the route depicted in Scheme 2. Unsubstituted or substituted pyridyl hydrazine **2** is reacted with unsubstituted or substituted benzoic acid **1** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl), 4-methylmorpholine and 1-hydroxybenzotriazole hydrate (HOBt), in anhydrous 1:1 dichloromethane/acetonitrile. Phosphorous oxychloride is then added to the solution of resulting compound **3** in toluene, and the compound of formula (IX) **4** is obtained.

The skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (IX) other than those depicted above.

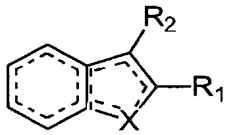
Illustrative compounds **145**, **147**, **149**, **151**, **153**, **155**, **157** and **159** are commercially available from Specs (http//:www.specsnet.com); compounds **163**, **165** and **167** are available from Chemdiv (http//www.chemdiv.com); compound **161** is available from Tripos (http://www.tripos.com); and compound **169** is available for purchase from Comgenex (http://www.comgenex.com).

5.3. The Use of the Edg-7 Compounds of the Invention

The present invention provides a method of modulating an LPA3 or Edg-7 receptor (e.g. human Edg-7, GenBank Accession No. AF127138) mediated biological activity. A cell expressing the Edg-7 receptor is contacted with an amount of an Edg-

7 receptor agonist or antagonist sufficient to modulate the Edg-7 receptor mediated biological activity.

The agonists or antagonists can be utilized in the methods of the present invention and are compounds of structural formula (XIII):



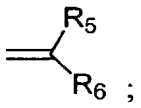
(XIII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

X is NR^3, S or O;

R_1 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, amino, carbamoyl, substituted carbamoyl, oxo, thiono or $-NR^4$; and

R_2 is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkyloxy, substituted alkyloxy, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl,



;

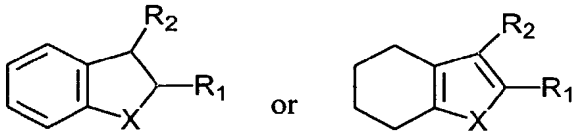
heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or

R_3 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl or substituted heteroalkyl;

R_4 is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heteroaryl substituted heteroaryl, cycloheteroalkyl, substituted cycloheteroalkyl, and

R_5 and R_6 are independently hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or optionally along with the carbon to which they are attached form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

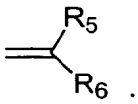
In a specific embodiment, the modulator is a compound of structural formula:



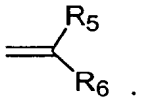
Preferably, R_1 is oxo, thiono or NR_4, more preferably, R_1 is oxo or NR_4. In one embodiment, R_4 is acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, carbamoyl or substituted carbamoyl. Preferably, R_4 is substituted carbamoyl..

In another embodiment, R_2 is acyl, substituted acyl, acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted

alkylarylamino, alkylsulfonyl, substituted alkylsulfonyl, aryloxycarbonyl, substituted aryloxycarbonyl, carbamoyl, substituted carbamoyl, or

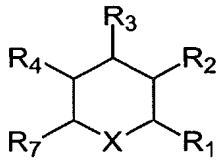


Preferably, R_2 is substituted alkoxycarbonyl or



Preferably, R_5 and R_6 along with the carbon to which they are attached form a cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring. More preferably, R_5 and R_6 along with the carbon to which they are attached form a substituted cycloheteroalkyl ring.

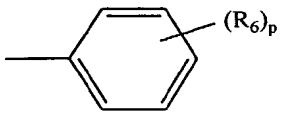
In another embodiment, the agonists or antagonists are also compounds of structural formula (XIV):



(XIV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein

each R_5 and R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -NH(aryl), -N=C(aryl), -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

X is CH_2, C=O, O, S, SO_2, C, or NR_5;

R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

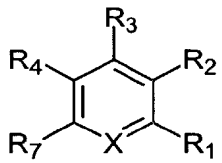
R_1, R_2, R_3 R_4 and R_7 can also be an electron such that when two groups are on adjacent carbon atoms they form a double bond;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In another embodiment, the modulator is a compound of structural formula (XV):

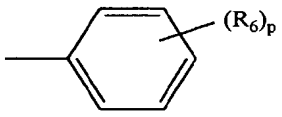


(XV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, -NO_2, -CN, -C(R_5)$_3$, -(CH_2)$_m$OH, -N(R_5)(R_5), -O(CH_2)$_m$$R_5$, -C(O)$R_5$, -C(O)N$R_5$$R_5$, -C(O)NH($CH_2$)$_m$($R_5$), -$OCF_3$, -benzyl, -$CO_2$CH($R_5$)($R_5$), -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl,

-(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -(C_5-C_{10})heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, -(C_1-C_{10})alkyl$NHC(O)(CH_2)_mR_5$, -(C_1-C_{10})alkylNR_5R_5,, $-S(O)_2N(R_5)C(O)NH$(heteroaryl), $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1$-$C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1$-$C_{10})$alkyl, $-C(O)(C_1$-$C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1$-$C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1$-$C_{10})$alkyl(C_1-C_{10})alkyl), $-CO_2(C_1$-$C_{10})$alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1$-$C_{10})$alkyl, $-NHC(O)NH(C_1$-$C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1$-$C_{10})$alkyl, or $-SO_2NH_2$;

X is C, or N;

R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

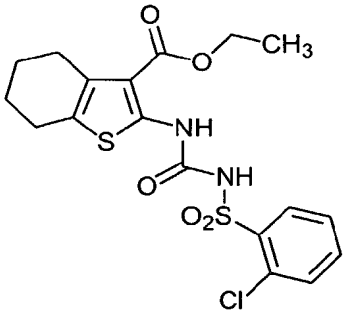
R_1, R_2, R_3 R_4 and R_7 can also be an electron such that when two groups are on adjacent carbon atoms they form a double bond;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In a specific embodiment, the compound is of formula:



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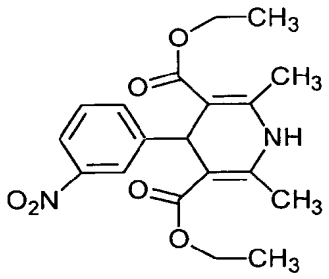

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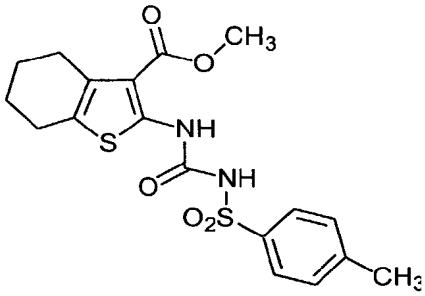

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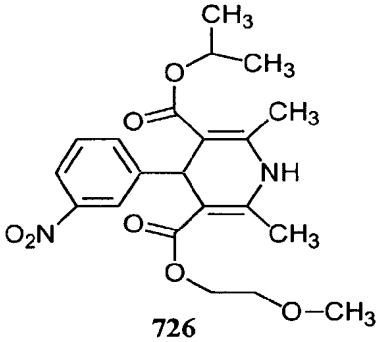

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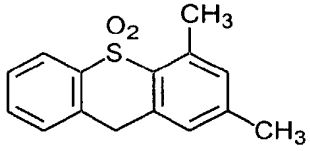

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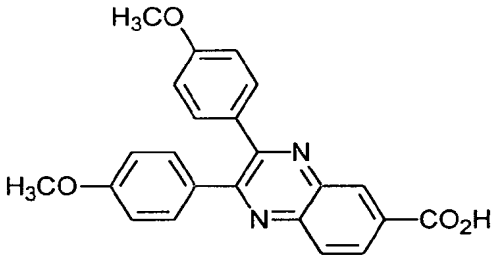

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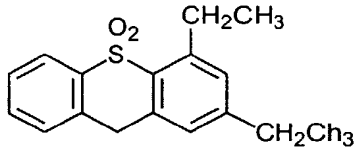

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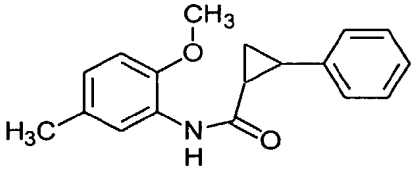

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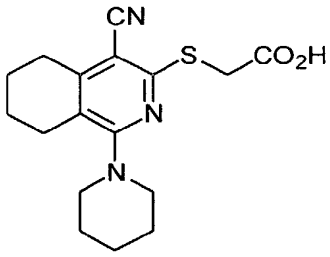
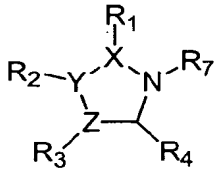


737

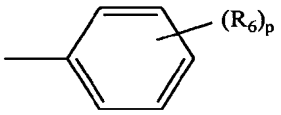
In another embodiment, the modulator is of structural formula (XVI):



(XVI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

X, Y, and Z are each independently C=O, O, S, C, or N; wherein if X, Y, or Z is O or S, R_1 is an electron pair;

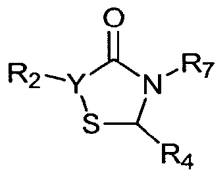
R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

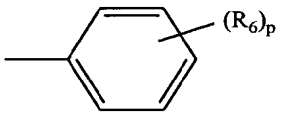
In another embodiment, the a modulator is of structural formula (XVII):



(XVII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4 and R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

X, Y, and Z are each independently C=O, O, S, C, or N; wherein if X, Y, or Z is O or S, R_1 is an electron pair;

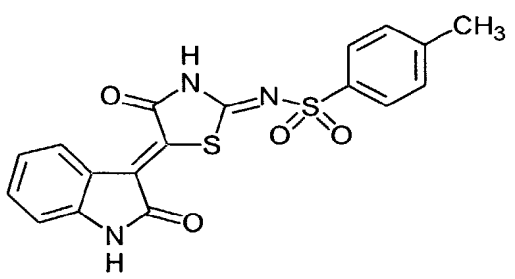
R_1, R_2, R_3 R_4 and R_7 taken in any combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In a specific embodiment, the modulator is of formula:



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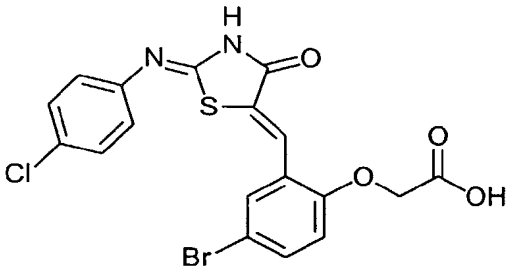

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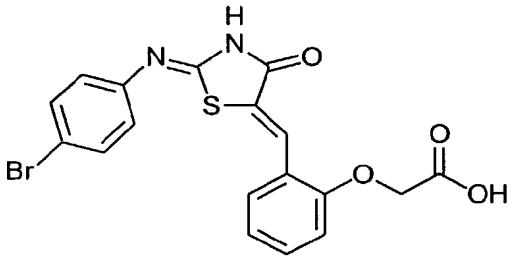

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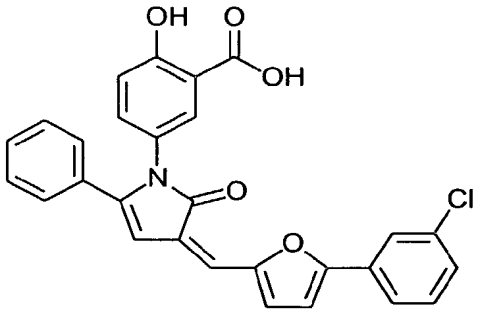

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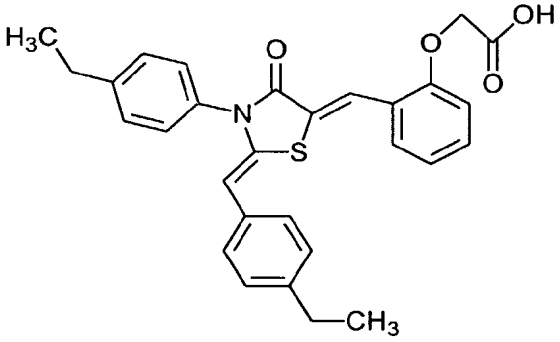

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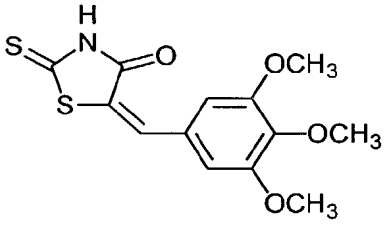

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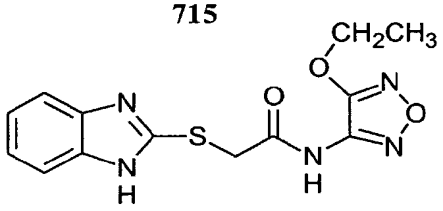

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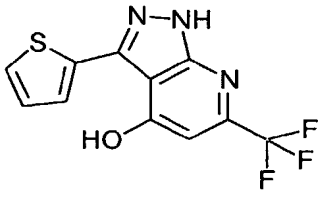

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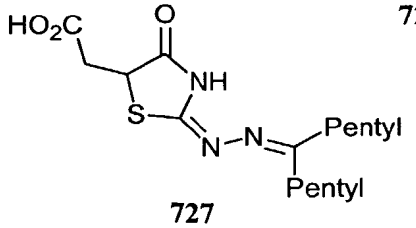


727

Those of skill in the art will appreciate that Edg-7 receptor is a G protein coupled receptor ("GPCR"). The Edg-7 (LPA3) receptor is encoded by an endothelial differentiation gene and along with related receptors, Edg-2 (LPA1) and Edg-4

(LPA2), binds lysophosphatidic acid ("LPA"). Preferably, the Edg-7 receptor is a human receptor.

The Edg-7 receptor may be expressed by recombinant DNA methods well known to those of skill in the art. Particularly useful cell types for expressing and assaying Edg-7 include, but are not limited to, HTC4 (rat hepatoma cells), RH7777 (rat hepatoma cells), HepG2 (human hepatoma cells), CHO (Chinese hamster ovary cells) and HEK-293 (human embryonic kidney cells). Particularly useful vectors for expressing G-protein receptors include, but are not limited to, pLXSN and pCMV (Clontech Labs, Palo Alto, CA; Invitrogen Corporation, Carlsbad, CA).

DNA encoding Edg-7 (human Edg-7, GenBank accession AF011466) can be transfected into human or mammalian cells according to methods known to those of skill in the art. For example, DNA encoding human Edg-7 can be co-transfected with a standard packaging vector, such as those described above, which provides an ecotropic envelope for viral replication, into a packaging cell line such as GP-293 (Clontech Labs, Palo Alto, CA).

Alternatively, DNA encoding Edg-7 can be transfected into the EcoPack-293 cell line which has, in addition to *gag* and *pol*, the *env* gene to produce an ecotropic envelope. Both methods (*i.e.*, co-transfection with a packaging vector or use of EcoPack-293) enable the production of an ecotropic envelope for viral packaging, and can thus advantageously be used to transfect rat and mouse cells. For use in human and other mammalian cells, AmphoPack-293 cell line can be used (Clontech Labs, Palo Alto, CA).

In addition, a number of natural cell lines naturally express Edg-7 receptors. These include, but are not limited to, CaOV-3 human ovarian cancer cells, MDA-MB-453 and MDA-MB-231 breast cancer cells, HT-1080 human fibrosarcoma, HUVEC cells and OV202 human ovarian cancer cells (ATCC, Manassas, VA; Vec Technologies Inc. (Rensselaer, NY); Dr. Edward Goetzl, University of California, San Francisco, San Francisco, CA).

Those of skill in the art will appreciate that cells which express the Edg-7 receptor may grown *in vitro* or may be part of a complex organism such as, for example, a mammal. It is contemplated that the methods of the current invention will be applicable to modulation of Edg-7 receptor activity, regardless of the local environment. In one preferred embodiment, cells that express the Edg-7 receptor are

grown *in vitro* (*i.e.*, are cultured). In another preferred embodiment, cells that express the Edg-7 receptor are *in vivo* (*i.e.*, are part of a complex organism).

The cells in which the method of the invention may be practiced include, but are not limited to, hepatoma cells, ovarian cells, epithelial cells, fibroblast cells, neuronal cells, cardiac myocytes, carcinoma cells, pheochromocytoma cells, myoblast cells, endothelial cells, platelet cells and fibrosarcoma cells. More specifically, the cells in which the invention may be practiced include, but are not limited to, OV202 human ovarian cells, hepatoma cells (e.g. HTC, Rh7777, HepG2), SKOV3 human ovarian cancer cells, CAOV-3 human ovarian cancer cells, HEY human ovarian cancer cells, HTC rat hepatoma cells, CAOV-3 human ovarian cancer cells, MDA-MB-453 breast cancer cells, MDA-MB-231 breast cancer cells, A431 human epitheloid carcinoma cells and HT-1080 human fibrosarcoma cells.

In a second aspect, an Edg-7 receptor mediated biological activity is modulated in a subject or in an animal model. A therapeutically effective amount of an modulator of the Edg-7 receptor is administered to the subject or animal. Preferably, the subject or an animal is in need of such treatment.

The biological activity mediated by the Edg-7 receptor may include, for example, calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP formation or actin polymerization. Preferably, the biological activity mediated by the Edg-7 receptor also includes, but is not limited to, apoptosis, angiogenesis, inhibition of wound healing, inflammation, cancer invasiveness or atherogenesis. Most preferably, the biological activity mediated by the Edg-7 receptor is cell proliferation, which may lead to ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer or prostrate cancer. In one embodiment, cell proliferation is stimulated by LPA.

In another embodiment, the biological activity mediated by the Edg-7 receptor may include increasing fatty acids levels (*e.g.*, free fatty acids and lyso-phosphatidylcholine) which may lead to acute lung diseases, such as adult respiratory distress syndrome ("ARDS") and acute inflammatory exacerbation of chronic lung diseases like asthma.

In yet another embodiment, compounds that block Edg-7 can be potentially effective immunosuppressive agents because activated T cells have Edg-7 receptors

(Zheng *et al.*, **2000**, *FASEB J* 14:2387-2389). Edg-7 antagonists may be useful in a variety of autoimmune and related immune disorders, including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura, and autoimmune hemolytic anemia. Additionally, Edg-7 antagonists can be used in organ transplantation.

In one embodiment, the modulator exhibits inhibitory selectivity for the Edg-7 receptor. For example, the modulator can exhibit at least about 200 fold inhibitory selectivity for Edg-7 relative to other Edg receptors. Inhibitory selectivity can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.4 (Example 4), 6.6 (Example 6) and 6.7 (Example 7) respectively. Other assays suitable for determining inhibitory selectivity would be known to one of skill in the art. Preferred assays include the calcium mobilization assay of Section 6.5.

In another embodiment, the modulator exhibits at least about 100 fold inhibitory selectivity for Edg-7 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 20 fold inhibitory selectivity for Edg-7 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-7 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 100 fold inhibitory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 20 fold inhibitory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In a preferred embodiment, an modulator of cell proliferation exhibits at least about 100 fold inhibitory selectivity for Edg-7 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 20 fold inhibitory selectivity for Edg-7 relative to other Edg receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 10 fold inhibitory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In another embodiment, the modulator exhibits stimulatory selectivity for the Edg-7 receptor. For example, the modulator can exhibit at least about 200 fold stimulatory selectivity for Edg-7 relative to other Edg receptors. Stimulatory selectivity can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.5 (Example 5), 6.7 (Example 7) and 6.8 (Example 8) respectively. Other assays suitable for determining stimulatory selectivity would be known to one of skill in the art. Preferred assays include the calcium mobilization assay of Section 6.5.

In another embodiment, the modulator exhibits at least about 100 fold stimulatory selectivity for Edg-7 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 20 fold stimulatory selectivity for Edg-7 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 10 fold stimulatory selectivity for Edg-7 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 200 fold stimulatory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 100 fold stimulatory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 20 fold stimulatory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In still another embodiment, the modulator exhibits at least about 10 fold stimulatory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In a preferred embodiment, an modulator of cell proliferation exhibits at least about 100 fold stimulatory selectivity for Edg-7 relative to other Edg receptors.

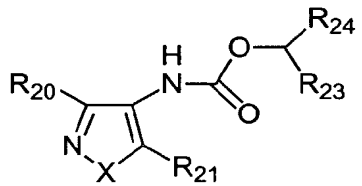
In another embodiment, the modulator of cell proliferation exhibits at least about 20 fold stimulatory selectivity for Edg-7 relative to other Edg receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 10 fold stimulatory selectivity for Edg-7 relative to Edg-2 and Edg-4 receptors.

In one embodiment, the Edg-7 modulator is not a lipid. In another embodiment, the Edg-7 modulator does not contain a phosphate group such as a

phosphoric acid, a cyclic phosphate ester or a linear phosphate ester. In another embodiment, the Edg-7 modulator is not a phospholipid. The term "phospholipid" includes all phosphate (both phosphate esters and phosphoric acids) containing glycerol derivatives with an alkyl chain of greater 10 carbon atoms or greater, any N-acyl ethanolamide phosphate derivative (both phosphate esters and phosphoric acids), LPA, S1P or any of their analogues (both phosphate esters and phosphoric acids) (see, *e.g.*, Bandoh, *et al.*, **2000**, *FEBS Lett.* 428, 759; Bittman et al., **1996**, *J. Lipid Research* 391; Lilliom *et al.*, **1996**, *Molecular Pharmacology* 616, Hooks *et al.*, **1998**, *Molecular Pharmacology* 188; Fischer *et al.*, **1998**, *Molecular Pharmacology* 979; Heise *et al.*, **2001**, *Molecular Pharmacology* 1173; Hopper *et al.*, **1999**, *J.Med.Chem.* 42 (6):963-970; Tigyi *et al.*, **2001**, *Molecular Pharmacology* 1161).

In another embodiment, the Edg-7 modulator is not a compound of structural formula (XVIII):



(XVIII)

or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

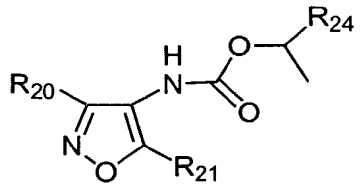
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

or alternatively R_{23} and R_{24} form a cycloalkyl ring (International Application No: WO 01/60819).

In another embodiment, the modulator is not any compound of the formula below:



wherein R_{20}, R_{21} and R_{24} are as previously defined. In yet another embodiment the modulator is not any compound disclosed in International Application No: WO 01/60819.

In one preferred embodiment, the modulator is a agonist of the Edg-7 receptor. The modulator can be a weaker agonist than the natural agonist and may compete with the natural agonist for the binding site. In another preferred embodiment, the modulator is antagonist of the Edg-7 receptor. The Edg-7 modulator may be a biomolecule such as a nucleic acid, protein, (*i.e.*, an enzyme or an antibody) or oligosaccharide or any combination thereof. Alternatively, the Edg-7 modulator may be oligomers or monomers of the above biomolecules such as amino acids, peptides, monosaccharides, disaccharides, nucleic acid monomers, dimers, *etc.*, or any combination thereof. The Edg-7 modulator may also be a synthetic polymer or any combination of synthetic polymer with biomolecules including monomers or oligomers of biomolecules.

The Edg-7 modulator may also be an organic molecule of molecular weight less than 750 daltons. In one embodiment, the molecular weight is about 200 to about 1000 daltons. In another embodiment, the molecular weight is about 200 to about 750 daltons. In yet another embodiment, the molecular weight is about 200 to about 500 daltons. Preferably, the molecular weight is about 300 to about 500 daltons.

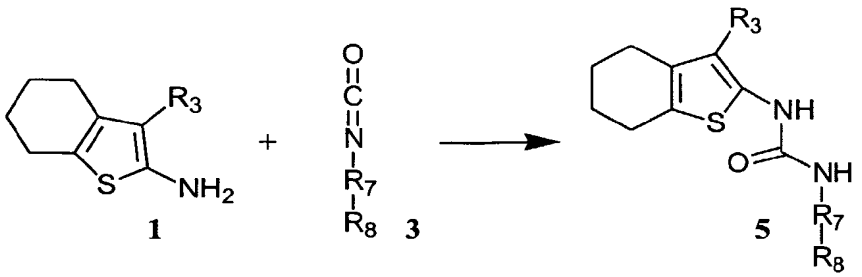
Without wishing to be bound by any particular theory or understanding, the modulator may, for example, facilitate inhibition of the Edg-7 receptor through direct binding to the LPA binding site of the receptor, binding at some other site of the Edg-7 receptor, interference with Edg-7 or LPA biosynthesis, covalent modification of either LPA or the Edg-7 receptor, or may otherwise interfere with Edg-7 mediated signal transduction.

In one embodiment, the agonist or antagonist binds to the Edg-7 receptor with a binding constant between about 10 μM and about 1 fM. In another embodiment, the modulator binds to the Edg-7 receptor with a binding constant between about 10 μM and about 1 nM. In another embodiment, the modulator binds to the Edg-7 receptor with a binding constant between about 1 μM and about 1 nM. In another embodiment, the modulator binds to the Edg-7 receptor with a binding constant between about 100 nM and about 1 nM. In another embodiment, the modulator binds to the Edg-7 receptor with a binding constant between about 10 nM and about 1 nM. Preferably, the modulator binds to the Edg-7 receptor with a binding constant better (*i.e.*, less) than about 10 nM.

5.4 Synthesis of the Edg-7 Compounds of the Invention

The compounds of the invention may be obtained *via* the synthetic methods illustrated in Schemes 3 and 4. Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods. Other methods for synthesis of the compounds described herein are either described in the art or will be readily apparent to the skilled artisan in view of general references well-known in the art (See *e.g.*, Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991); Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-17, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," John Wiley & Sons, 1995) and may be used to synthesize the compounds of the invention. Accordingly, the methods presented in Schemes 3 and 4 herein are illustrative rather than comprehensive.

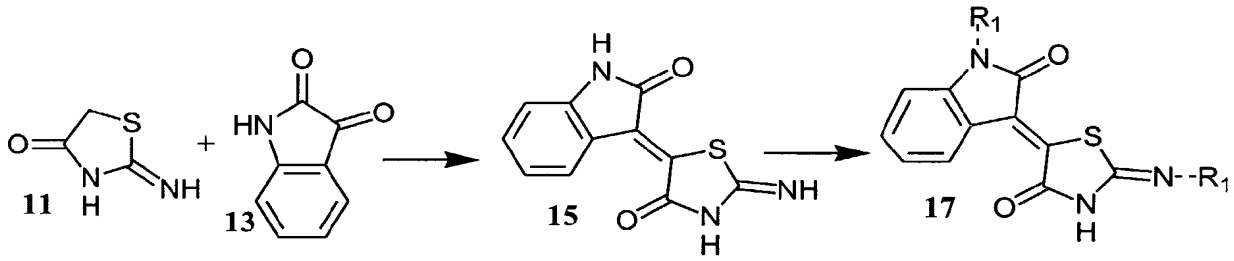
Scheme 3



The compounds depicted in Schemes 3 and 4 are compounds of structural formula (I). Generally, compounds of structural formula (I) may be made by the route depicted in Scheme 1. Reaction of amine **1** with isocyanate **3** in the presence of organic solvents, (*e.g.*, benzene) provides substituted urea **5**.

Those of skill in the art will appreciate that a large number of analogues of **5** may be prepared simply by using different amines **1** and/or isocyanates **3**. In addition, those of skill in the art will appreciate that a wide variety of compounds other than the isocyanate **3** depicted may be reacted with amine 1 to provide compounds of the invention. Further the skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (I) other than those depicted above.

Scheme 4



As shown in Scheme 4 above, addition of pseudothiohydantoin **11** to isatin **13** in the presence of acid and salt (*e.g.*, acetic acid and sodium acetate) provides indolone **15** which may be alkylated, arylated, acylated or sulfonated by treatment with appropriate compounds to provide indolone **17**. The alkylation, arylation, acylation or sulfontion can take place at either or both of the location indicated with a dashed bond.

Those of skill in the art will appreciate that a large number of analogues of **17** may be prepared simply by using different alkylation, arylation, acylation or sulfontion agents. Further the skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (I) other than those depicted above.

Illustrative compounds **709**, **713**, **715** and **723** are also commercially available from Specs (http//www.specs.net); illustrative compound **719** is commercially available from Asinex; illustrative compound **725** is commercially available from Tripos. Illustrative compounds **701**, **711**, and **719** are commercially available from Asinex. Illustrative compounds **717** is available from Labotest. Illustrative compound **727** is commercially available from Chemdiv. Illustrative compounds **729**, **733**, **735**, and **737** are commercially available from Specs.

5.5 The Use of the Edg-2 Compounds of the Invention

The present invention provides a method of modulating an LPA1 or Edg-2 receptor (*e.g.*, human Edg-2, GenBank Accession No., U78192) mediated biological activity. A cell expressing the Edg-2 receptor is contacted with an amount of an Edg-2 receptor agonist or antagonist sufficient to modulate the Edg-2 receptor mediated biological activity.

Those of skill in the art will appreciate that the Edg-2 receptor is a G protein coupled receptor. The Edg-2 (LPA1) receptor is encoded by an endothelial differentiation gene and along with related receptors, Edg-4 (LPA2) and Edg-7 (LPA3), binds lysophosphatidic acid ("LPA"). Preferably, the Edg-2 receptor is a human receptor.

The Edg-2 receptor may be expressed by recombinant DNA methods well known to those of skill in the art. Particularly useful cell types for expressing and assaying Edg-2 include, but are not limited to, HTC4 (rat hepatoma cells), RH7777 (rat hepatoma cells), HepG2 (human hepatoma cells), CHO (Chinese hamster ovary cells) and HEK-293 (human embryonic kidney cells). Particularly useful vectors for expressing G-protein receptors include, but are not limited to, pLXSN and pCMV (Clontech Labs, Palo Alto, CA; Invitrogen Corporation, Carlsbad, CA).

DNA encoding Edg-2 is well known (*e.g.*, human Edg-2, GenBank Accession No., U78192) and can be transfected into human or mammalian cells according to methods known to those of skill in the art. For example, DNA encoding human Edg-

2 can be co-transfected with a standard packaging vector, such as those described above, which provides an ecotropic envelope for viral replication, into a packaging cell line such as GP-293 (Clontech Labs, Palo Alto, CA).

Alternatively, DNA encoding Edg-2 can be transfected into the EcoPack-293 cell line which has, in addition to *gag* and *pol*, the *env* gene to produce an ecotropic envelope. Both methods (*i.e.* co-transfection with a packaging vector or use of EcoPack-293) enable the production of an ecotropic envelope for viral packaging, and can thus advantageously be used to transfect rat and mouse cells. For use in human and other mammalian cells, AmphoPack-293 cell line can be used (Clontech Labs, Palo Alto, CA).

In addition, a number of natural cell lines naturally express Edg-2 receptors. These include, but are not limited to, CaOV-3 human ovarian cancer cells, MDA-MB-453 and MDA-MB-231 breast cancer cells, HT-1080 human fibrosarcoma, HUVEC cells and OV202 human ovarian cancer cells (ATCC, Manassas, VA; Vec Technologies Inc. (Rensselaer, NY); Dr. Edward Goetzl, University of California, San Francisco, San Francisco, CA).

Those of skill in the art will appreciate that cells which express the Edg-2 receptor may grown *in vitro* or may be part of a complex organism such as, for example, a mammal. It is contemplated that the methods of the current invention will be applicable to modulation of the Edg-2 receptor activity regardless of the local environment. In one preferred embodiment, cells that express the Edg-2 receptor are grown *in vitro* (*i.e.*, are cultured). In another preferred embodiment, cells that express the Edg-2 receptor are *in vivo* (*i.e.*, are part of a complex organism).

The cells, in which the method of the invention may be practiced include, but are not limited to, hepatoma cells, ovarian cells, epithelial cells, fibroblast cells, neuronal cells, cardiac myocytes, carcinoma cells, pheochromocytoma cells, myoblast cells, endothelial cells, platelet cells and fibrosarcoma cells. More specifically, the cells in which the invention may be practiced include, but are not limited to, OV202 human ovarian cell, HTC rat hepatoma cells, CAOV-3 and SKOV-3 human ovarian cancer cells, MDA-MB-453 breast cancer cells, MDA-MB-231 breast cancer cells, A431 human epitheloid carcinoma cells and HT-1080 human fibrosarcoma cells.

In a second aspect, an Edg-2 receptor mediated biological activity is modulated in a subject or in an animal model. A therapeutically effective amount of

an modulator of the Edg-2 receptor is administered to the subject or an animal. Preferably, the subject or animal is in need of such treatment.

The biological activity mediated by the Edg-2 receptor may include, for example, calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP formation or actin polymerization. Preferably, the biological activity mediated by the Edg-2 receptor includes, but is not limited to, apoptosis, angiogenesis, inhibition of wound healing, inflammation, cancer invasiveness or atherogenesis. Most preferably, the biological activity mediated by the Edg-2 receptor is cell proliferation, which may lead to ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colon cancer or prostrate cancer. In one embodiment, cell proliferation is stimulated by LPA.

In another embodiment, the biological activity mediated by the Edg-2 receptor may include increasing fatty acids levels (*e.g.*, free fatty acids and lyso-phosphatidylcholine) which may lead to acute lung diseases, such as adult respiratory distress syndrome ("ARDS") and acute inflammatory exacerbation of chronic lung diseases like asthma.

In yet another embodiment, compounds that block Edg-2 can be potentially effective immunosuppressive agents because activated T cells have Edg-2 receptors (Zheng *et al.*, **2000**, *FASEB J* 14:2387-2389). Edg-2 antagonists may be useful in a variety of autoimmune and related immune disorders, including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura, and autoimmune hemolytic anemia. Additionally, Edg-2 antagonists can be used in organ transplantation.

In one embodiment, the modulator exhibits selectivity for the Edg-2 receptor. For example, the modulator exhibits at least about 5 to about 200 fold inhibitory selectivity for Edg-2 relative to other Edg receptors. Inhibitory selectivity, can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.8 (Example 8), 6.10 (Example 10) and 6.11 (Example 11) respectively. In a preferred embodiment, inhibitory selectivity can be measured by a calcium mobilization assay.

Other assays suitable for determining inhibitory selectivity would be known to one of skill in the art.

In another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-2 relative to other non-Edg receptors, GPCRs, growth factor receptors, ion channels and the like.

In another embodiment, the modulator exhibits at least about 40 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 12 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 5 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 40 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 12 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 5 inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In a preferred embodiment, an modulator of cell proliferation exhibits at least about 200 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 5 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 200 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 5 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In another embodiment, the modulator exhibits activating selectivity for the Edg-2 receptor. For example, the modulator exhibits at least about 5 to about 200 fold activating selectivity for Edg-2 relative to other Edg receptors. Activating selectivity, can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in

Section 6.8 (Example 8), 6.10 (Example 10) and 6.11 (Example 11) respectively. In a preferred embodiment, activating selectivity can be measured by a calcium mobilization assay. Other assays suitable for determining activating selectivity would be known to one of skill in the art.

In another embodiment, the modulator exhibits at least about 200 fold activating selectivity for Edg-2 relative to other non-Edg receptors, GPCRs, growth factor receptors, ion channels and the like.

In another embodiment, the modulator exhibits at least about 40 fold activating selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 12 fold activating selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 5 fold activating selectivity for Edg-2 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 200 fold activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 40 fold activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 12 fold activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator exhibits at least about 5 activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In a preferred embodiment, an modulator of cell proliferation exhibits at least about 200 fold activating selectivity for Edg-2 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 5 fold activating selectivity for Edg-2 relative to other Edg receptors.

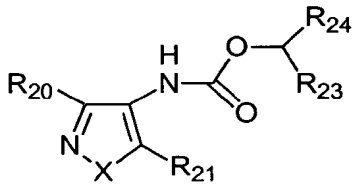
In still another embodiment, the modulator of cell proliferation exhibits at least about 200 fold activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 5 fold activating selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

In one embodiment, the Edg-2 modulator is not a lipid. In another embodiment, the modulator of Edg-2 modulator does not contain a phosphate group such as a phosphoric acid, a cyclic phosphate ester or a linear phosphate ester. In

another embodiment, the Edg-2 modulator is not a phospholipid. The term "phospholipid" includes all phosphate (both phosphate esters and phosphoric acids) containing glycerol derivatives with an alkyl chain of 10 carbon atoms or greater, dioctyl glycerol, any N-acyl ethanolamide phosphate derivative (both phosphate esters and phosphoric acids), LPA, S1P or any of their analogues (both phosphate esters and phosphoric acids) (see, *e.g.*, Bandoh, *et al.*, **2000**, *FEBS Lett.* 428, 759; Bittman et al., **1996**, *J. Lipid Research* 391; Lilliom *et al.*, **1996**, *Molecular Pharmacology* 616, Hooks *et al.*, **1998**, *Molecular Pharmacology* 188; Fischer *et al.*, **1998**, *Molecular Pharmacology* 979; Heise *et al.*, **2001**, *Molecular Pharmacology* 1173; Hopper *et al.*, **1999**, *J.Med.Chem.* 42 (6):963-970; Tigyi *et al.*, **2001**, *Molecular Pharmacology* 1161).

In another embodiment, the Edg-2 modulator is not a compound of the formula:



or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

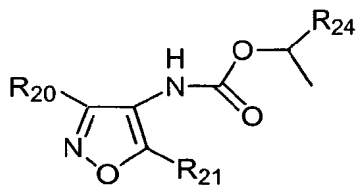
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

or alternatively R_{23} and R_{24} form a cycloalkyl ring (International Application No: WO 01/60819).

In another embodiment, the modulator is not any compound of the formula below:



wherein R_{20}, R_{21} and R_{24} are as previously defined. In yet another embodiment the modulator is not any compound disclosed in International Application No: WO 01/60819.

In one embodiment, the Edg-2 modulator is an agonist of the Edg-2 receptor. In one aspect, such an embodiment provides an Edg-2 modulator that is an agonist, but is a weaker agonist than a natural Edg-2 agonist (*e.g.*, LPA) and as such, may compete with the natural agonist for Edg-2 binding site, resulting in a net inhibition of Edg-2 receptor activity.

In another preferred embodiment, the modulator is antagonist of the Edg-2 receptor. The Edg-2 modulator may be a biomolecule such as a nucleic acid, protein (*e.g.*, an enzyme, an antibody or a soluble Edg-2 receptor polypeptide) or oligosaccharide or any combination thereof. Alternatively, the Edg-2 modulator may be oligomers or monomers of the above biomolecules such as amino acids, peptides, monosaccharides, disaccharides, nucleic acid monomers, dimers, *etc.*, or any combination thereof. The Edg-2 modulator may also be a synthetic polymer or any combination of synthetic polymer with biomolecules including monomers or oligomers of biomolecules.

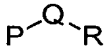
The Edg-2 modulator may also be a small organic molecule. In particular embodiments, such a small organic molecule exhibits a molecular weight about 200 to about 1000 daltons, about 200 to about 750 daltons, 200 to about 500 daltons, or about 300 to about 500 daltons. In a particularly preferred embodiment, the small organic molecule can be orally administered to a subject. In another preferred embodiment, the small organic molecule is capable of crossing the blood-brain barrier.

Without wishing to be bound by any particular theory or understanding, the modulator may, for example, facilitate inhibition of the Edg-2 receptor through direct binding to the LPA binding site of the receptor, binding at some other site of the Edg-2 receptor, interference with Edg-2 or LPA biosynthesis, covalent modification

of either LPA or the Edg-2 receptor, or may otherwise interfere with Edg-2 mediated signal transduction.

In one embodiment, the agonist or antagonist binds to the Edg-2 receptor with a binding constant between about 10 μM and 1 fM. In another embodiment, the agonist or antagonist binds to the Edg-2 receptor with a binding constant between about 10 μM and about 1 nM. In another embodiment, the agonist or antagonist binds to the Edg-2 receptor with a binding constant between about 1 μM and about 1 nM. In another embodiment, the agonist or antagonist binds to the Edg-2 receptor with a binding constant between about 100 nM and about 1 nM. In another embodiment, the agonist or antagonist binds to the Edg-2 receptor with a binding constant between about 10 nM and about 1 nM. Preferably, the agonist or antagonist binds to the Edg-2 receptor with a binding constant better (*i.e.*, less) than about 10 nM.

Preferably, the Edg-2 modulator has the structural formula (XX):



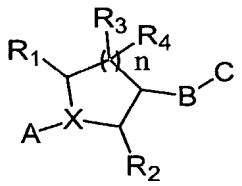
(XX)

or a pharmaceutically available salt, hydrate or solvate thereof wherein:

P, Q and R are independently aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl.

In one preferred embodiment, Q is cycloheteroalkyl, substituted cycloheteroalkyl and P and R are independently aryl or substituted aryl. In another preferred embodiment, Q is cycloheteroalkyl or substituted cycloheteroalkyl and P and R are independently phenyl or substituted phenyl. In still another preferred embodiment, Q is heteroaryl or substituted heteroaryl and P and R are independently aryl or substituted aryl. In still another preferred embodiment, Q is heteroaryl or substituted heteroaryl and P and R are independently phenyl or substituted phenyl.

In a preferred embodiment, the Edg-2 modulator has the structural formula (XXI):



(XXI)

wherein:

n is 1, 2 or 3;

X = N or CH;

R_1 and R_2 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cyano, cyanato, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxo or thiono;

R_3 and R_4 are independently hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, halo or thio;

B is NR_5, O or S;

R_5 is hydrogen, alkyl, substituted alkyl, alkylamino, substituted alkylamino, alkoxy, substituted alkoxy, amino, cyano, dialkylamino, substituted dialkylamino or hydroxy; and

A and C are independently aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl.

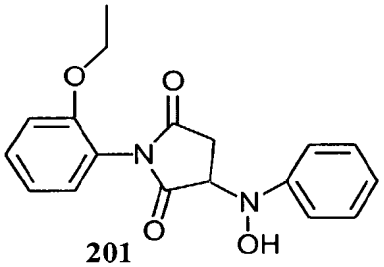
Preferably, R_1 and R_2 are independently hydrogen, alkyl substituted alkyl, oxo or thiono. More preferably, R_1 and R_2 are independently oxo or thiono. In one preferred embodiment, R_3 and R_4 are independently hydrogen or alkyl.

Preferably, A and C are independently aryl, substituted aryl, heteroaryl or substituted heteroaryl. More preferably, A and C are aryl or substituted aryl. Most preferably, A and C are phenyl or substituted phenyl.

In one embodiment, B is NR_5 and R_5 is hydrogen, alkyl or hydroxy. In another embodiment, n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5 and R_5 is hydroxy.

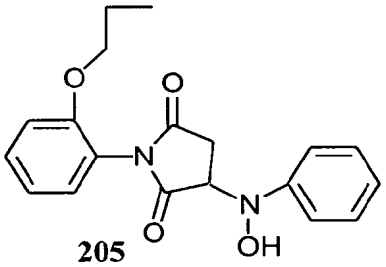
In another preferred embodiment, n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5, R_5 is hydroxy, A and B are aryl or substituted aryl. In still another preferred embodiment, n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5, R_5 is hydroxy, A and B are phenyl or substituted phenyl.

The Edg-2 modulators can also include the following compounds.



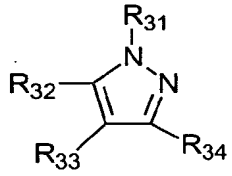
201

or



205

In another preferred embodiment, the modulator has the structural formula (XXII):



(XXII)

wherein:

R_{31} is hydrogen, alkyl or substituted alkyl;

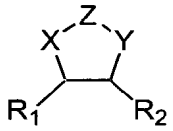
R_{32} is hydrogen, alkyl or substituted alkyl;

R_{33} is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_{34} is aryl, substituted aryl, heteroaryl or substituted heteroaryl.

In one embodiment, R_{31} and R_{32} are alkyl. In another embodiment, R_{33} and R_{34} are aryl or substituted aryl. In still another embodiment, R_{31} and R_{32} are alkyl and R_{33} and R_{34} are aryl or substituted aryl. In still another embodiment, R_{33} and R_{34} are phenyl or substituted phenyl. In still another embodiment, R_{31} and R_{32} are methyl or ethyl and R_{33} and R_{34} are phenyl or substituted phenyl.

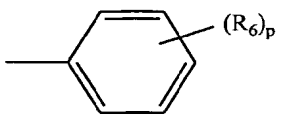
In another embodiment, the Edg-2 modulator has the structural formula (XXIII):



(XXIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

X, Y, and Z are each independently $C(R_5)(R_5)$, C(O), O, C(S), S, $C{=}N(R_5)$, or NR_3;

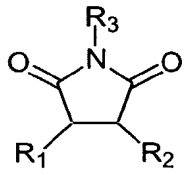
each m is independently an integer ranging from 0 to 8;

each p is independently an integer ranging from 0 to 5; and

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

In one preferred embodiment, X and Y are both O. In another preferred embodiment, R_1 is –N(OH)aryl.

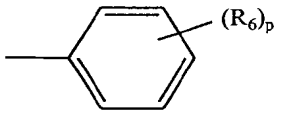
In a preferred embodiment, the Edg-2 modulator has the structural formula (XXIV):



(XXIV)

wherein:

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, $-(C_5-C_{10})heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each of R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

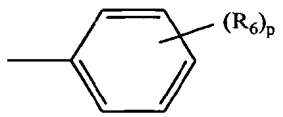
each m is independently an integer ranging from 0 to 8;

each p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and X or R_2 and Y can together form a double bond.

Preferably, R_1 is -H, and R_2 and R_3 are independently $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, $-(C_5-C_{10})heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, or

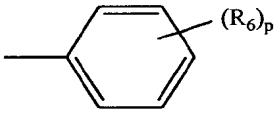


wherein;

each of R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-O(C_1-C_{10})alkyl$,

-C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;
each m is independently an integer ranging from 0 to 8;
each p is independently an integer ranging from 0 to 5.

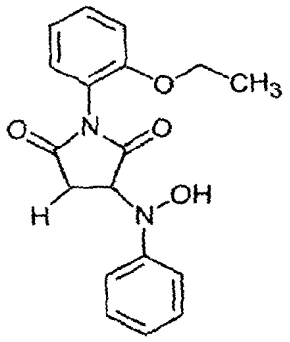
More preferably, R_1 is –H and R_2 and R_3 are



wherein;

each R_6 is independently -halo, -NO_2, -CN, -OH, -CO_2H, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;
each m is independently an integer ranging from 0 to 8;
each p is independently an integer ranging from 0 to 5.

The Edg-2 modulators can also include the following compounds:



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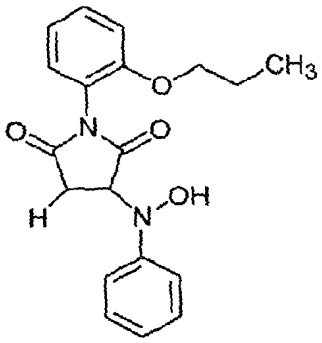
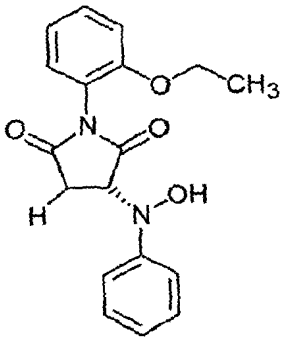
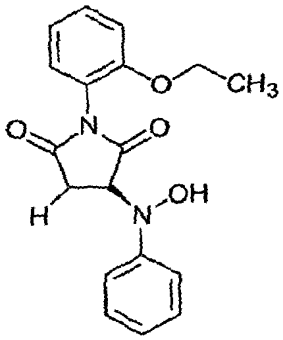


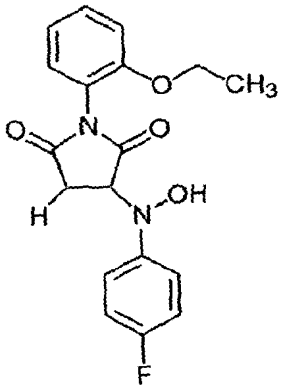
205



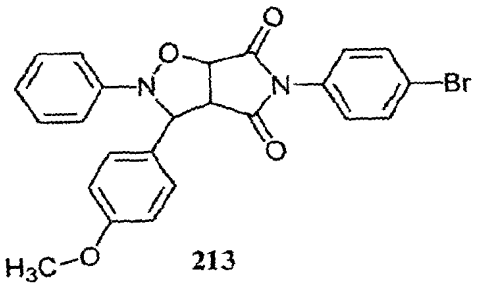
207



209



211



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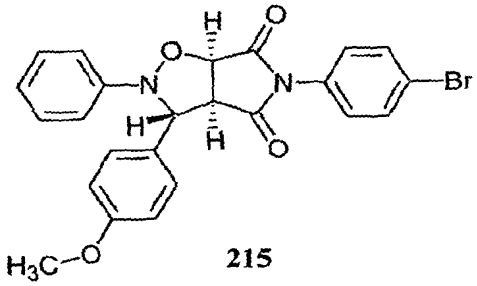
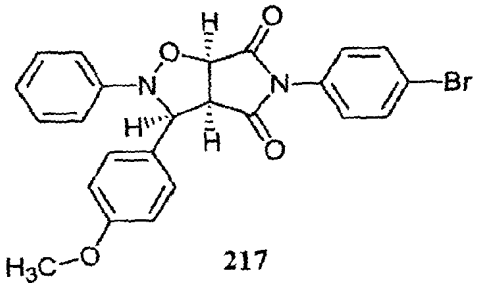
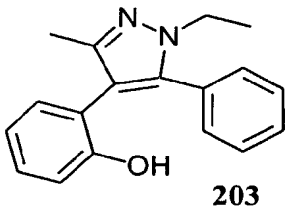


215



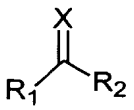
217

A preferred Edg-2 modulator is a compound of the formula below:



203

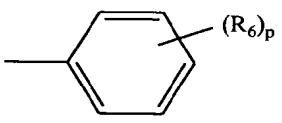
In another embodiment, the Edg-2 modulators have the structural formula (XXV):



(XXV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -NH(aryl), -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, -aryl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_3\text{-}C_{10})$cycloalkyl(aryl), $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

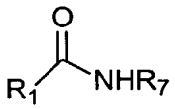
R_1 and R_2 can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

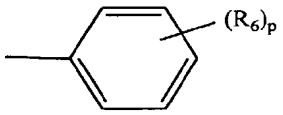
The Edg-2 modulator can also preferably be a compound of the structural formula (XXVI):



(XXVI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

R_1 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, $-(C_5-C_{10})heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-OC(O)aryl$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

R_7 is $-CO_2H$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$,

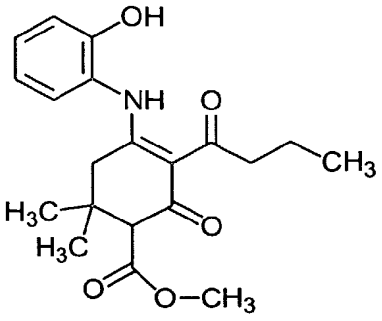
R_1 and R_2 can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

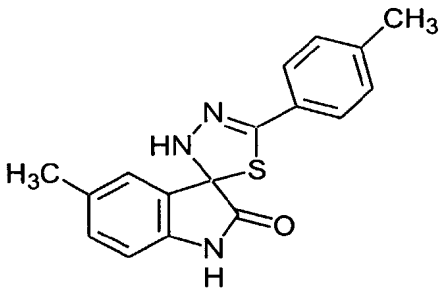
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

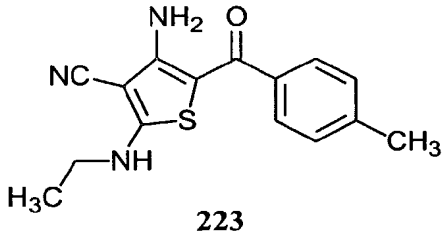
The Edg-2 modulators can also include the following compounds:



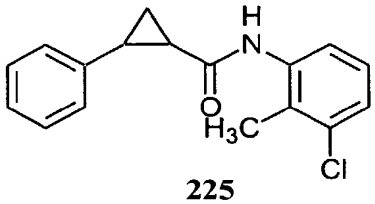
219



221

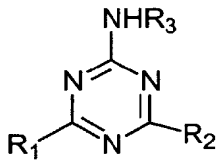


223



225

In one embodiment, the Edg-2 modulators of the invention have the structural formula (XXVII):

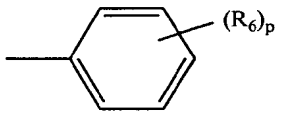


(XXVII)

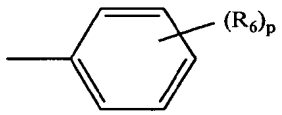
or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$,

$-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, -OC(O)aryl, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

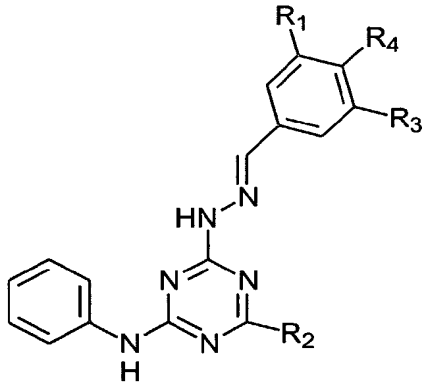
each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In one preferred embodiment, R_3 is –N=C(aryl). In another preferred embodiment, R_1 is –NH(aryl).

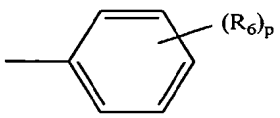
In a preferred embodiment, the Edg-2 modulator has the structural formula (XXVIII):



(XVIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_4 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-OC(O)$aryl, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



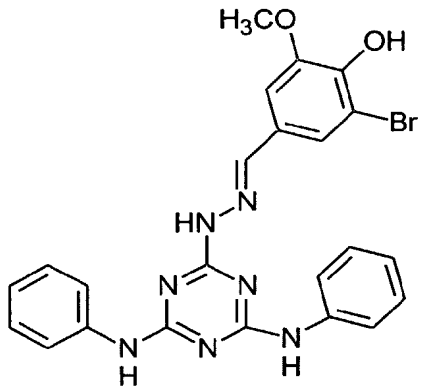
wherein;

each R_5 and R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -NH(aryl), -N=C(aryl), -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

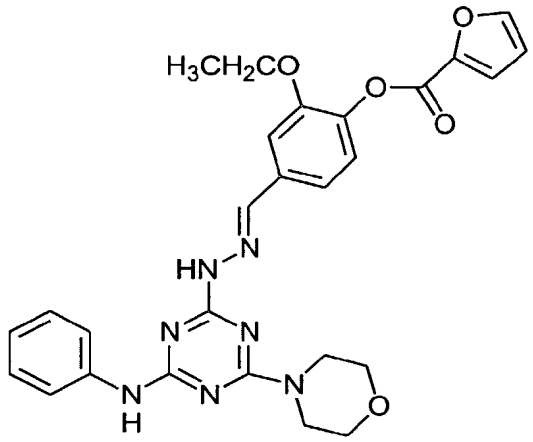
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

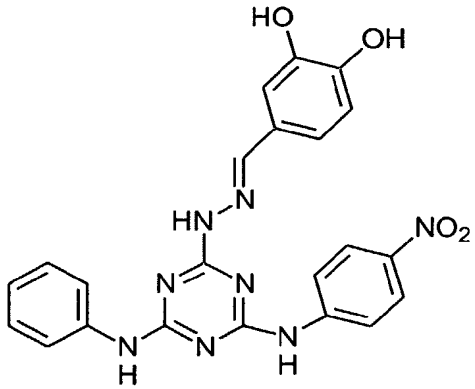
The Edg-2 modulators can also include the following compounds:



227



229



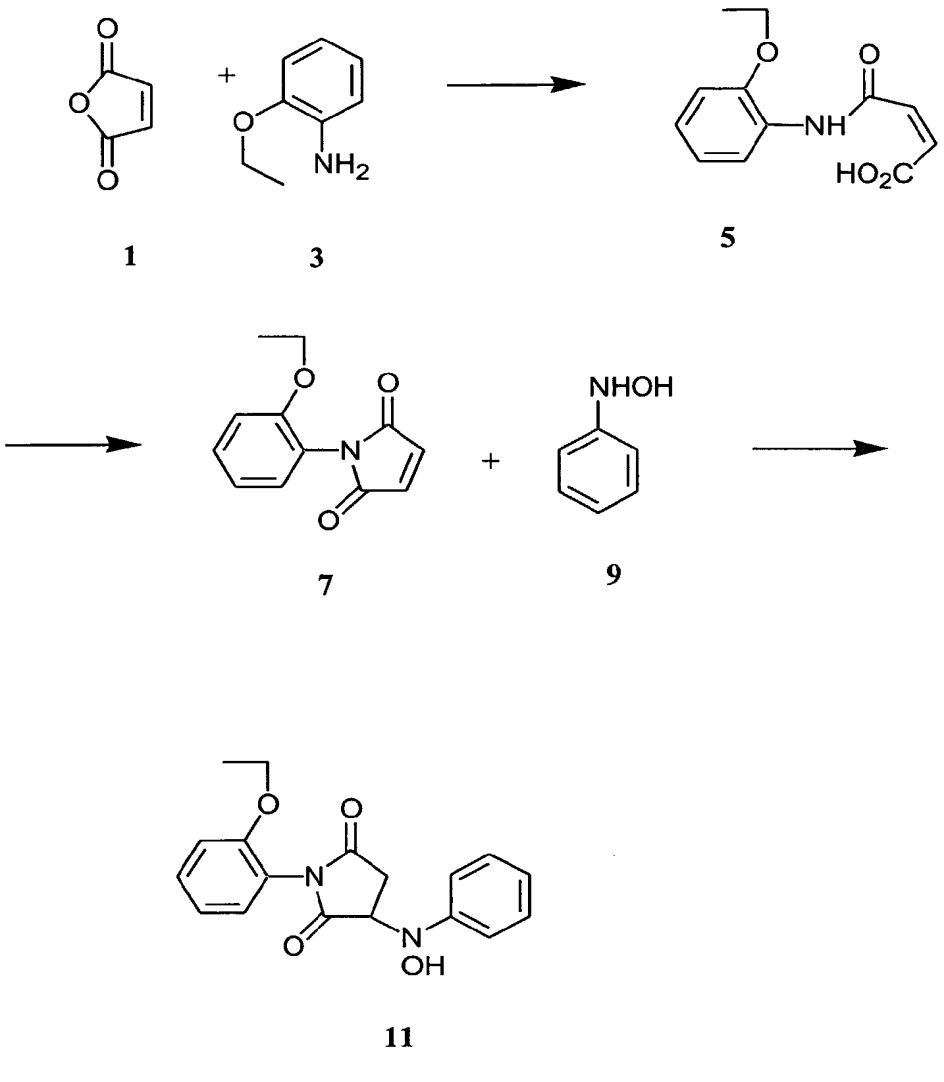
231

5.6 Synthesis of the Edg-2 Compounds of the Invention

Compounds of the invention, and intermediates thereof, are commercially available or can be prepared by well-known synthetic methods. Schemes 5 and 6 exemplify synthetic methods for preparing compounds of the invention. Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods. Other methods for synthesis of the compounds described herein are either described in the art or will be readily apparent to the skilled artisan in view of general references well-known in the art (See *e.g.*, Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991); Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-17, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," John Wiley & Sons, 1995) and may be used to synthesize the compounds of the invention. Accordingly, the methods presented in Schemes 5 and 6 herein are illustrative rather than comprehensive. In addition, compounds of formula **227**, **229**, and **231** are commercially available from Chemical Diversity Labs, Inc. (San Diego, CA).

The compounds depicted in Schemes 1 and 2 are compounds of structural formula (II). Compounds of structural formula (II) may be made by the route depicted in these Schemes.

Scheme 5



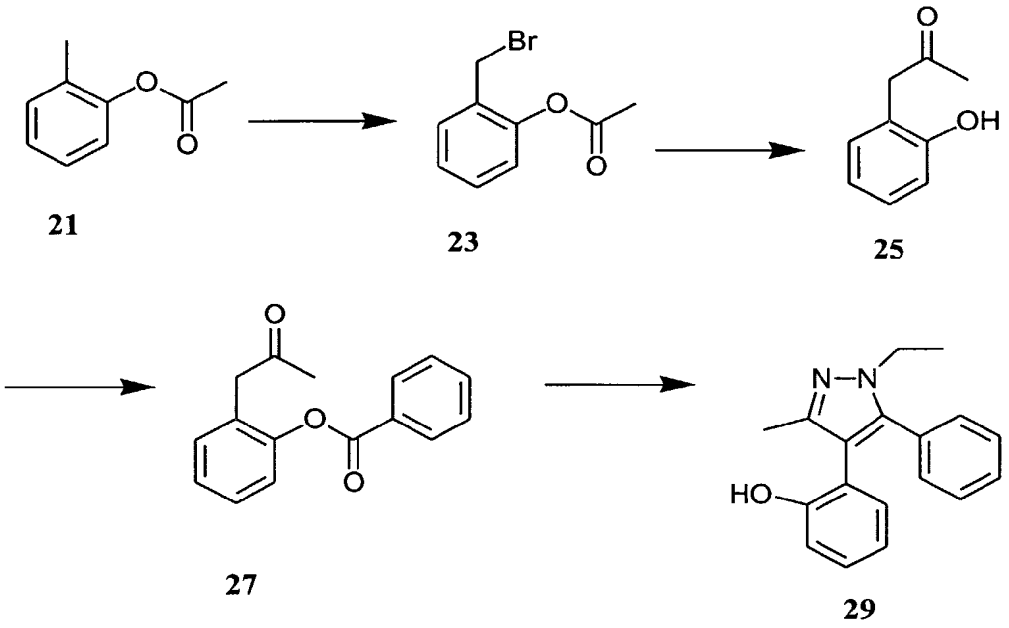
1 3 5

7 9

11

As shown above in Scheme 5, Michael addition of aromatic amine **3** to maleic anhydride **1** provides amide **5**, which may be cyclized (*e.g.*, sodium acetate and acetic anhydride) to yield imide **7**. Michael addition of phenylhydroxylamine, which may be prepared from nitrobenzene by partial reduction (*e.g.*, Zn, NH_4Cl) gave the desired disubstituted imide **11**. Those of skill in the art will appreciate that a large number of analogues of **11** may be prepared simply by using different amines **3** and/or hydroxylamines other than phenyl hydroxylamine.

Scheme 6



21 **23** **25** **27** **29**

As shown in Scheme 6 above, free radical bromination of acylated phenol **21** (*e.g.*, NBS, AIBN) gave bromide **23**, which may be converted to ketone **25** ($CrCl_2$) by internal acyl transfer. Ketone **25** may be acylated to provide benzoate **27**, (*e.g.*, benzoyl chloride, dimethylaminopyridine) which can undergo cyclization to give pyrazole **29** (*e.g.*, ethylhydrazine, acetic acid). Those of skill in the art will appreciate that many analogues may be simply prepared by using a different acylating agent or by staring with a different acyl phenol.

5.7 The Use of the Edg-3 Compounds of the Invention

The present invention provides a method of modulating an S1P3 or Edg-3 receptor (e.g., human Edg-3, GenBank Accession No. X83864) mediated biological activity. A cell expressing the Edg-3 receptor is contacted with an amount of an Edg-

3 receptor agonist or antagonist sufficient to modulate an Edg-3 receptor mediated biological activity.

Those of skill in the art will appreciate that Edg-3 is a G protein coupled receptor ("GPCR"). The Edg-3 (S1P3) receptor is encoded by an endothelial differentiation gene and along with related receptors, Edg-1 (S1P1), Edg-5 (S1P2), Edg-6 (S1P4) and Edg-8 (S1P5), binds sphingosine-1-phosphate ("S1P"). Preferably, the Edg-3 receptor is a human receptor.

The Edg-3 receptor may be expressed by recombinant DNA methods well known to those of skill in the art. Particularly useful cell types for expressing and assaying Edg-3 include, but are not limited to, HTC4 (rat hepatoma cells), RH7777 (rat hepatoma cells), HepG2 (human hepatoma cells), CHO (Chinese hamster ovary cells) and HEK-293 (human embryonic kidney cells). Particularly useful vectors for expressing G-protein receptors include, but are not limited to, pLXSN and pCMV (Clontech Labs, Palo Alto, CA; Invitrogen Corporation, Carlsbad, CA).

DNA encoding Edg-3 is well known (e.g., human Edg-3, GenBank Accession No. X83864) and can be transfected into human or mammalian cells according to methods known to those of skill in the art. For example, DNA encoding human Edg-3 can be co-transfected with a standard packaging vector, such as those described above, which provides an ecotropic envelope for viral replication, into a packaging cell line such as GP-293 (Clontech Labs, Palo Alto, CA).

Alternatively, DNA encoding Edg-3 can be transfected into the EcoPack-293 cell line which has, in addition to *gag* and *pol*, the *env* gene to produce an ecotropic envelope. Both methods (*i.e.*, co-transfection with a packaging vector or use of EcoPack-293) enable the production of an ecotropic envelope for viral packaging, and can thus advantageously be used to transfect rat and mouse cells. For use in human and other mammalian cells, AmphoPack-293 cell line can be used (Clontech, Palo Alto, CA).

A number of natural cell lines naturally express Edg-3 receptors. These include, but are not limited to, CaOV-3 human ovarian cancer cells, MDA-MB-453 and MDA-MB-231 breast cancer cells, HT-1080 human fibrosarcoma, HUVEC cells, OV202 human ovarian cancer cells, Hela human cervical adenocarcinoam cells, HEK293 human embryonic kidney cells, NIH 3T3 mouse fibroblast cells (ATCC, Manassas, VA; Vec Technologies Inc., Rensselaer, NY; Dr. Edward Goetzl, University of California, San Francisco, San Francisco, CA).

Those of skill in the art will appreciate that cells which express the Edg-3 receptor may grown *in vitro* or may be part of a complex organism such as, for example, a mammal. It is contemplated that the methods of the current invention will be applicable to modulating, *e.g.*, agonizing or antagonizing, Edg-3 receptor activity, regardless of the local environment. In one preferred embodiment, cells that express the Edg-3 receptor are grown *in vitro* (*i.e.*, are cultured). In another preferred embodiment, cells that express the Edg-3 receptor are *in vivo* (*i.e.*, are part of a complex organism).

The cells in which the method of the invention may be practiced include, but are not limited to, hepatoma cells, ovarian cells, epithelial cells, fibroblast cells, neuronal cells, cardiac myocytes, carcinoma cells, pheochromocytoma cells, myoblast cells, platelet cells, endothelial cells, keratinocytes and fibrosarcoma cells. More specifically, the cells in which the invention may be practiced include, but are not limited to, OV202 human ovarian cells, HTC rat hepatoma cells, CAOV-3 and SKOV-3 human ovarian cancer cells, MDA-MB-453 breast cancer cells, MDA-MB-231 breast cancer cells, HUVEC, Hela human cervical adenocarcinoam cells, HEK293 human embryonic kidney cells, NIH 3T3 mouse fibroblast cells, A431 human epitheloid carcinoma cells, and HT-1080 human fibrosarcoma cells.

In a second aspect of the invention, an Edg-3 receptor mediated biological activity is modulated in a subject or in an animal model. A therapeutically effective amount of an modulator of the Edg-3 receptor is administered to the subject or animal. Preferably, the subject or animal is in need of such treatment.

The biological activity mediated by the Edg-3 receptor may include, for example, calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP formation or actin polymerization. Preferably, the biological activity mediated by the Edg-3 receptor also includes, but is not limited to, apoptosis, angiogenesis, wound healing, inflammation, expression of endogenous protein growth factors, cancer invasiveness or atherogenesis. Most preferably, the biological activity mediated by the Edg-3 receptor is cell proliferation, which may lead to enhancement of wound healing; alternatively, it may lead ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer or prostrate cancer. In one embodiment, cell proliferation is stimulated by S1P.

In another embodiment, the biological activity mediated by the Edg-3 receptor may include increasing fatty acids levels (*e.g.*, free fatty acids and lyso-phosphatidylcholine) which may lead to acute lung diseases, such as adult respiratory distress syndrome ("ARDS") and acute inflammatory exacerbation of chronic lung diseases like asthma.

In yet another embodiment, the present invention provides methods for using Edg-3 antagonists in treating or preventing disorders such as, but not limited to, vasoconstriction in cerebral arteries, autoimmune and related immune disorders, including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura, and autoimmune hemolytic anemia. Additionally, Edg-3 antagonists can also be used in organ transplantation. Without intending to be bound by any particular mechanism or theory of action, Edg-3 antagonists are believed to be potentially effective immunosuppresive agents because activated T cells express the Edg-3 receptor.

In yet another embodiment, Edg-3 agonists and antagonists can be used to treat vascular occlusive disorders. For example, activation of Edg-3 receptors by using an Edg-3 agonist can result in increased vasoconstriction, which is beneficial in conditions such as migraine headaches. Inhibition of Edg-3 by an Edg3 antagonist can be beneficial in conditions such as a stroke, a subarachnoid hemorrhage, or a vasospasm such as a cerebral vasospasm.

In certain aspects, the modulator exhibits inhibitory selectivity for the Edg-3 receptor. In one embodiment, the modulator exhibits at least about 5 fold inhibitory selectivity for Edg-3 relative to other Edg receptors. Inhibitory selectivity can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.4 (Example 4), 6.6 (Example 6) and 6.7 (Example 7) respectively. Other assays suitable for determining inhibitory selectivity would be known to one of skill in the art. Preferred assays include the calcium mobilization assay of Section 6.4.

In another embodiment, the modulator exhibits at least about 20 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 100 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits about 5 fold to about 200 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 5 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 20 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 100 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits about 5 fold to about 200 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In a preferred embodiment, the modulator of cell proliferation exhibits at least about 5 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 20 fold inhibitory selectivity for Edg-3 relative to other Edg receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 5 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 20 fold inhibitory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In other aspects, the modulator exhibits stimulatory selectivity for the Edg-3 receptor. In one embodiment, the modulator exhibits at least about 5 fold stimulatory selectivity for Edg-3 relative to other Edg receptors. Stimulatory selectivity can be measured by assays such as a calcium mobilization assay or a migration and/or invasion assay or a proliferation assay, for example, as described in Section 6.4 (Example 4), 6.6 (Example 6) and 6.7 (Example 7) respectively. Other assays suitable for determining stimulatory selectivity would be known to one of skill in the art. Preferred assays include the calcium mobilization assay of Section 6.4.

In another embodiment, the modulator exhibits at least about 20 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 100 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 200 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator exhibits at least about 200 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In still another embodiment, the modulator exhibits about 5 fold to about 200 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In still another embodiment, the modulator exhibits at least about 5 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 20 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 100 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits at least about 200 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator exhibits about 5 fold to about 200 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In a preferred embodiment, the modulator of cell proliferation exhibits at least about 5 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

In another embodiment, the modulator of cell proliferation exhibits at least about 20 fold stimulatory selectivity for Edg-3 relative to other Edg receptors.

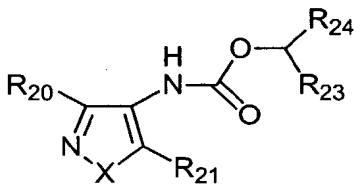
In still another embodiment, the modulator of cell proliferation exhibits at least about 5 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In still another embodiment, the modulator of cell proliferation exhibits at least about 20 fold stimulatory selectivity for Edg-3 relative to Edg-1, Edg-5, Edg-6 and Edg-8 receptors.

In certain embodiments, the Edg-3 modulator is not a lipid. In certain embodiments, the modulator of Edg-3 receptor mediated biological activity does not contain a phosphate group such as a phosphoric acid, a cyclic phosphate ester or a

linear phosphate ester. In certain embodiments, the modulator of the Edg-3 receptor is not a phospholipid. The term "phospholipid" includes all phosphate (both phosphate esters and phosphoric acids) containing glycerol derivatives with an alkyl chain of greater 10 carbon atoms or greater, dioctyl glycerol, any N-acyl ethanolamide phosphate derivative (both phosphate esters and phosphoric acids), LPA, S1P or any of their analogues (both phosphate esters and phosphoric acids) (see, *e.g.*, Bandoh, *et al.*, **2000**, *FEBS Lett.* 428, 759; Bittman et al., **1996**, *J. Lipid Research* 391; Lilliom *et al.*, **1996**, *Molecular Pharmacology* 616, Hooks *et al.*, **1998**, *Molecular Pharmacology* 188; Fischer *et al.*, **1998**, *Molecular Pharmacology* 979; Heise *et al.*, **2001**, *Molecular Pharmacology* 1173; Hopper *et al.*, **1999**, *J.Med.Chem.* 42 (6):963-970; Tigyi *et al.*, **2001**, *Molecular Pharmacology* 1161).

In certain embodiments, the modulator is also not a compound of structural formula (XXXIV):



(XXXIV)

or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

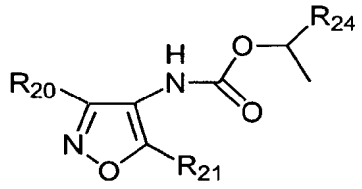
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

or alternatively R_{23} and R_{24} form a cycloalkyl ring (International Application No: WO 01/60819).

In certain embodiments, the modulator is not any compound of the formula below:



wherein R_{20}, R_{21} and R_{24} are as previously defined. In yet another embodiment the modulator is not any compound disclosed in International Application No: WO 01/60819.

In certain embodiments, the modulator can be an agonist of the Edg-3 receptor. The agonist can be a weaker agonist than the natural agonist and may compete with the natural agonist for the binding site. In other embodiments, the modulator can be an antagonist of the Edg-3 receptor.

In certain aspects, the Edg-3 modulator can be a biomolecule such as a nucleic acid, protein, (*e.g.*, an enzyme, an antibody, or a soluble Edg-3 receptor polypeptide) or oligosaccharide or any combination thereof. Alternatively, the Edg-3 modulator may be oligomers or monomers of the above biomolecules such as amino acids, peptides, monosaccharides, disaccharides, nucleic acid monomers, dimers, *etc.*, or any combination thereof. The Edg-3 modulator may also be a synthetic polymer or any combination of synthetic polymer with biomolecules including monomers or oligomers of biomolecules.

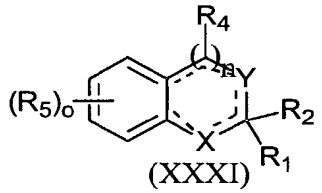
The Edg-3 modulator may also be a small organic molecule. In certain embodiments, the Edg-3 modulator can be an organic molecule of molecular weight less than 750 daltons. In other embodiments, the molecular weight can be about 200 to about 1000 daltons. In other embodiments, the molecular weight can be about 200 to about 750 daltons. In yet other embodiments, the molecular weight can be about 200 to about 600 daltons. In certain preferred embodiments, the molecular weight is about 300 to about 500 daltons. In certain embodiments, the small organic molecule can be orally administered to a subject. In other embodiments, the small organic molecule is capable of crossing the blood-brain barrier.

Without wishing to be bound by any particular theory or understanding, the modulator may, for example, facilitate inhibition of the Edg-3 receptor through direct

binding to the LPA binding site of the receptor, binding at some other site of the Edg-3 receptor, interfering with Edg-3 or LPA biosynthesis, covalently modifying either the LPA or the Edg-3 receptor, or otherwise interfering with Edg-3 mediated signal transduction.

In one embodiment, the modulator binds to the Edg-3 receptor with a binding constant between about 10 μM and about 1 fM. In another embodiment, the modulator binds to the Edg-3 receptor with a binding constant between about 10 μM and about 1 nM. In another embodiment, the modulator binds to the Edg-3 receptor with a binding constant between about 1 μM and about 1 nM. In another embodiment, the modulator binds to the Edg-3 receptor with a binding constant between about 100 nM and about 1 nM. In another embodiment, the modulator binds to the Edg-3 receptor with a binding constant between about 10 nM and about 1 nM. Preferably, the modulator binds to the Edg-3 receptor with a binding constant better (*i.e.*, less) than about 10 nM.

In certain embodiments, the modulator is a compound of structural formula (XXXI):



(XXXI)

or a pharmaceutically available solvate or hydrate thereof, wherein:

n = 0 or 1;

o is 0, 1, 2, 3 or 4;

X is C, NR^7 O or S;

Y is C, NR^8 O or S;

R_1 is either absent or hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio,

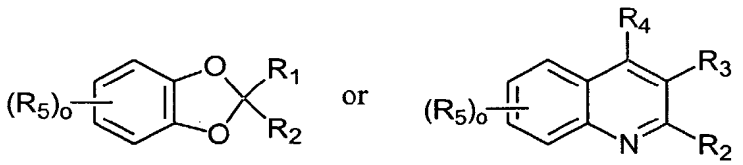
substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

R_2, R_3 and R_4 are independently hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

each R_5 is independently, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro or thio; and

$R_7$and R_8 are independently absent, hydrogen, alkyl, substituted alkyl, acyl or substituted acyl.

In other embodiments, the modulator is a compound of structural formula (XXXV) or structural formula (XXXVI):



(XXXV) (XXXVI)

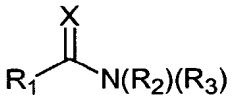
In one embodiment, R_1 is either absent or hydrogen, acyl, substituted acyl, acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, arylalkyloxy, substituted arylalkyloxy, carbamoyl, substituted carbamoyl, dialkylamino, substituted dialkylamino, heteroalkyl, or substituted heteroalkyl. Preferably, R_1 is either absent or acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, arylamino substituted arylamino, or carbamoyl, substituted carbamoyl. More preferably, R_1 is either absent or acylamino, substituted acylamino, arylamino or substituted arylamino.

In another embodiment, R_2, R_3 and R_4 are independently alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, carbamoyl, substituted carbamoyl, dialkylamino, substituted dialkylamino, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl. Preferably, R_2, R_3 and R_4 are independently alkyl, substituted alkyl, acylamino, substituted acylamino, aryl, substituted aryl, arylamino, substituted arylamino, carbamoyl or substituted carbamoyl. More preferably, R_2, R_3 and R_4 are independently alkyl, substituted acylamino, aryl, substituted arylamino or substituted carbamoyl.

In another embodiment, each R_5 is independently, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, amino, aryl, substituted aryl, azido, carboxy, carbamoyl, substituted carbamoyl, cyano, halo, hydroxyl, nitro or thio. Preferably, each R_5 is independently, alkyl, substituted alkyl,

alkoxy, substituted alkoxy, amino, azido, carboxy, carbamoyl, substituted carbamoyl, cyano, halo, hydroxyl, nitro or thio. Preferably, $R_7$and R_8 are independently absent, hydrogen, alkyl.

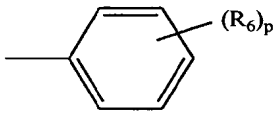
In still other embodiments, the modulator is a compound of structural formula (XXXII):



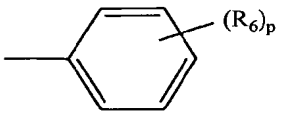
(XXXII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

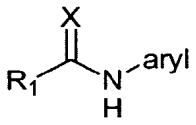
X is O, S, $C(R_5)(R_5)$ or $N(R_5)$;

R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

In another embodiment, the modulator is a compound of structural formula (XXXVII):



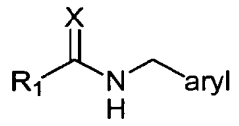
(XXXVII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

R_1 is hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkylarylamino, substituted alkylarylamino, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylamino, substituted arylamino, arylalkyl, substituted arylalkyl, dialkylamino, substituted alkyl amino, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl sulfonylamino or substituted sulfonylamino; and

X = O or S.

In yet other embodiments, the Edg-3 receptor modulator is a compound of structural formula (XXXVIII):



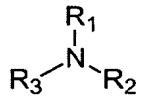
(XXXVIII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

R_1 is hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkylarylamino, substituted alkylarylamino, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylamino, substituted arylamino, arylalkyl, substituted arylalkyl, dialkylamino, substituted alkyl amino, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl sulfonylamino or substituted sulfonylamino; and

X = O.

In yet other embodiments, the Edg-3 receptor modulator has the structural formula (XXXIII):

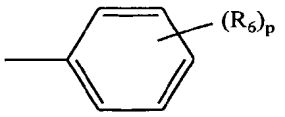


(XXXIII)

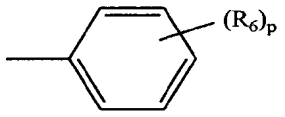
or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5,

$-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

X is O, S, or $N(R_5)$;

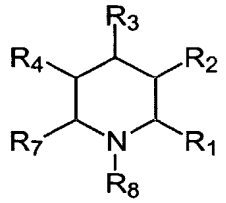
R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

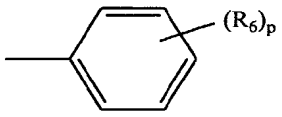
In still other embodiments, the Edg-3 receptor modulator is a compound of structural formula (XXXIX):



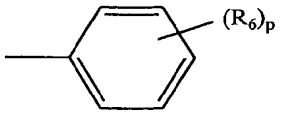
(XXXIX)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4, R_7 and R_8 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -heterocylcoalkyl, -$C(S)N(R_5)(R_5)$, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



R_3 is -H -$C(R_5)_3$, -$(CH_2)_mOH$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -NH(aryl), -N=C(aryl), -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

X is O, S, or N(R_5);

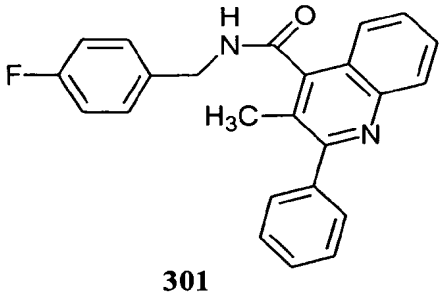
R_1 and R_2, R_2 and R_3, R_3 and R_4, R_4 and R_7, or R_7 and R_8 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

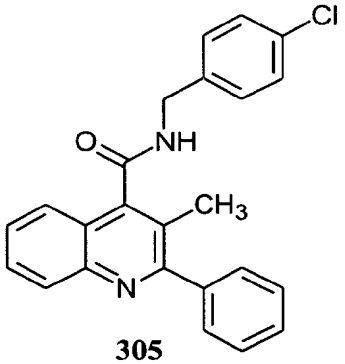
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

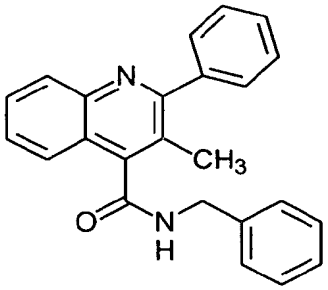
Preferred Edg-3 modulators include the following compounds:



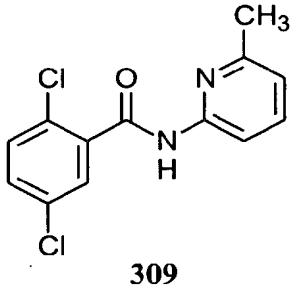
301



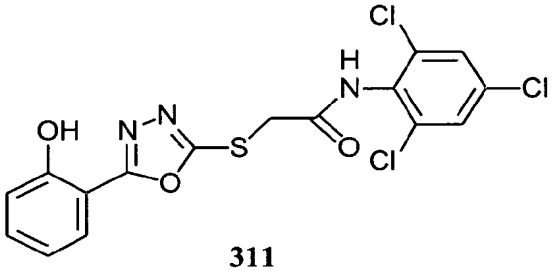
305



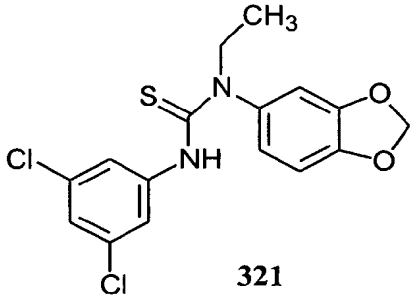
307



309

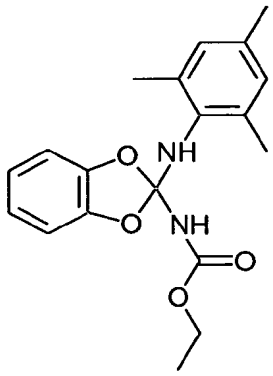


311



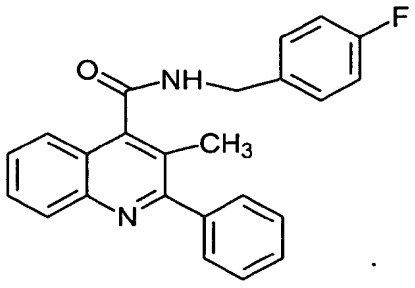
321

Preferred Edg-3 receptor modulators also include the following compounds:



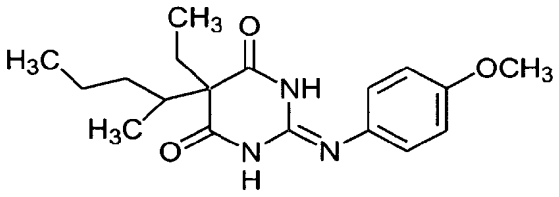
303

or

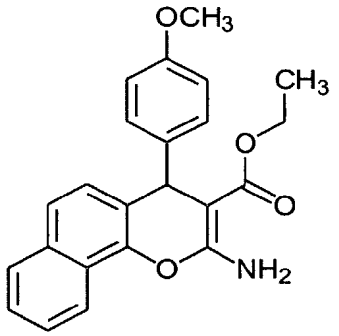


301

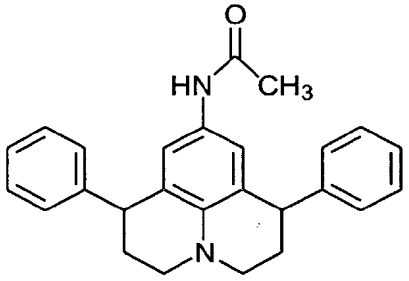
Preferred Edg-3 receptor modulators also include the following compounds:



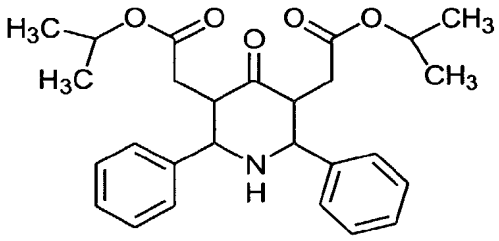
313



315



317



319

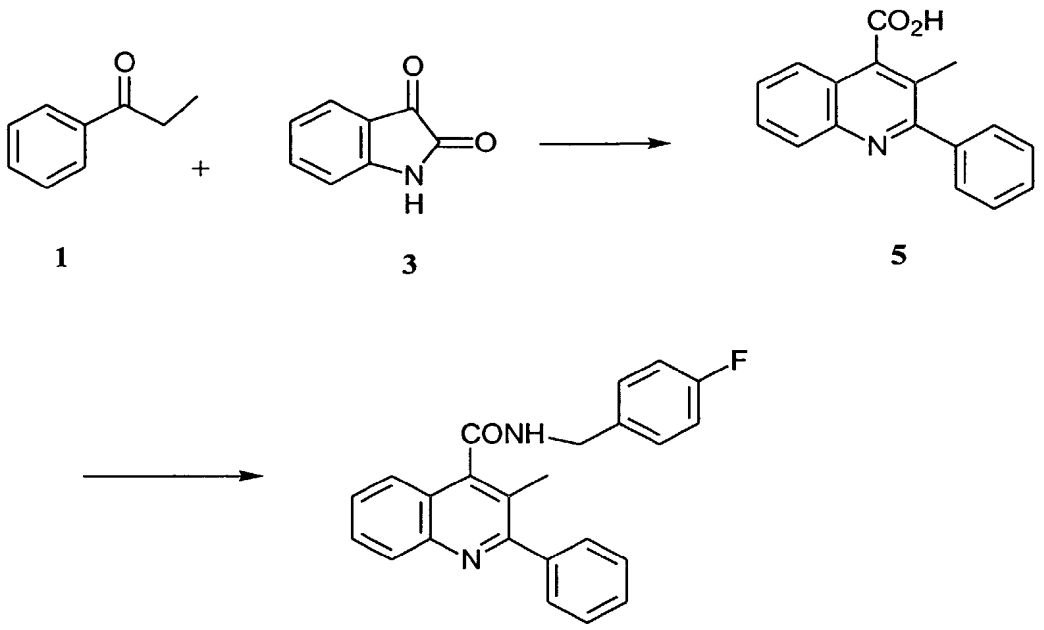
5.8 Synthesis of the Edg-3 Compounds of the Invention

The compounds of the invention may be obtained *via* the synthetic methods illustrated in Schemes 7, 8, and 9. Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods. Other methods for synthesis of the compounds described herein are either described in the art or will be readily apparent to the skilled artisan in view of general references well-known in the art (See *e.g.*, Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991); Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-17, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," John Wiley & Sons, 1995) and may be used to synthesize the

compounds of the invention. Accordingly, the methods presented in 7, 8 and 9 herein are illustrative rather than comprehensive.

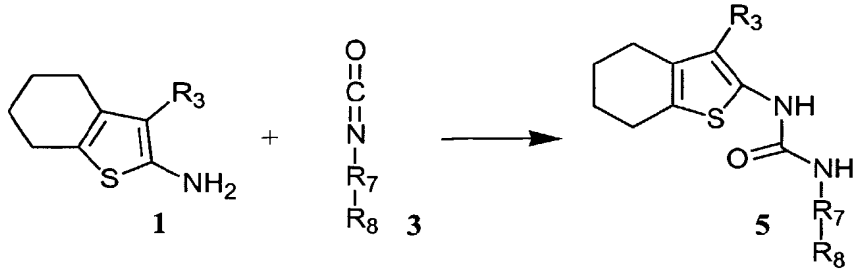
The route described in Scheme 7 may used to synthesize compounds of Formula (XXXI).

Scheme 7



Condensation of propiophenone **1** with isatin **3** (*i.e.*, Pfitzinger reaction, KOH, ethanol, heat) provided quinoline **5**, which was then acylated with fluoroamine **301** (*i.e.*, carbodiimide, HOBT) to give amide **301**. Those of skill in the art will appreciate that a wide variety of analogues of amide **301** may be made by simply reacting substituted propiophenones with substituted isatins and/or acylating the resulting quinoline with different arylamines.

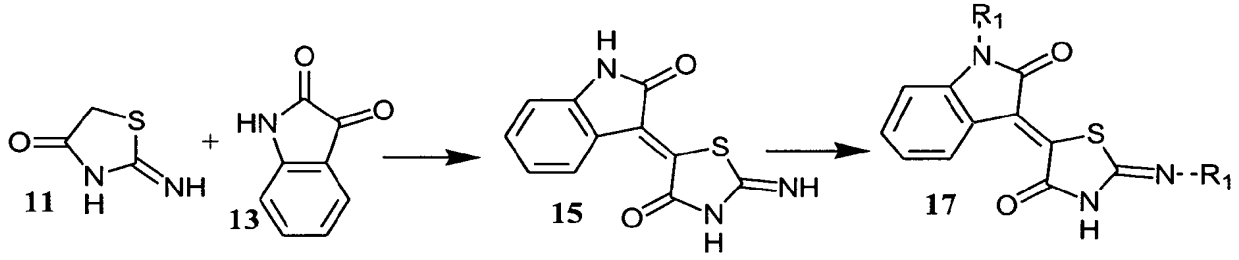
Scheme 8



The compounds depicted in Schemes 8 and 9 are compounds of structural formula (XXXII). Generally, compounds of structural formula (XXXII) may be made by the route depicted in Scheme 2. Reaction of amine **1** with isocyanate **3** in the presence of organic solvents, (*e.g.*, benzene) provides substituted urea **5**.

Those of skill in the art will appreciate that a large number of analogues of **5** may be prepared simply by using different amines **1** and/or isocyanates **3**. In addition, those of skill in the art will appreciate that a wide variety of compounds other than the isocyanate **3** depicted may be reacted with amine **1** to provide compounds of the invention. Further the skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (XXXII) other than those depicted above.

Scheme 9



As shown in Scheme 3 above, addition of pseudothiohydantoin **11** to isatin **13** in the presence of acid and salt (*e.g.*, acetic acid and sodium acetate) provides indolone **15** which may be alkylated, arylated, acylated or sulfonated by treatment with appropriate compounds to provide indolone **17**. The alkylation, arylation, acylation or sulfontion can take place at either or both of the location indicated with a dashed bond.

Those of skill in the art will appreciate that a large number of analogues of **17** may be prepared simply by using different alkylation, arylation, acylation or sulfontion agents. Further the skilled artisan will appreciate that a wide variety of conventional synthetic methods may be used to synthesize compounds of structural Formula (II) other than those depicted above.

Illustrative compounds **305, 307,** and **309** are commercially available from Specs. Illustrative compounds **301, 311, 313, 315, 319,** and **121** are commercially available from Asinex. Compound **317** is commercially available from Chemdiv.

5.9. Therapeutic Uses of the Compounds of the Invention

The compounds and/or compositions of the present invention may be used to treat diseases, including but not limited to, ovarian cancer (Xu *et al.*, **1995**, *Biochem. J.* 309 (Pt 3):933-940; Xu *et al.*, **1998**, *JAMA* 280 (8):719-723; Goetzl *et al.*, **1999**, *Cancer Res.* 59 (20):5370-5375), peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer and prostrate cancer; acute lung diseases, adult respiratory distress syndrome ("ARDS"), acute inflammatory exacerbation of chronic lung diseases such as asthma (Chilton *et al.*, **1996**, *J Exp Med* 183:2235-45; Arbibe *et al.*, **1998**, *J Clin. Invest* 102:1152-60) surface epithelial cell injury, *(e.g.,* transcorneal freezing or cutaneous burns (Liliom *et al.*, **1998**, *Am. J. Physiol* 274 (4 Pt 1*):* C1065-C1074)), cardiovascular diseases, *(e.g.,* ischemia (Karliner *et al.*, **2001**, *J. Mol Cell Cardiol.* 33 (9):1713-1717) and athescierosis (Siess *et al.*, **1999**, *Proc. Natl. Acad. Sci. U.S.A* 96 (12):6931-6936; Siess *et al.*, **2000**, *IUBMB.B Life* 49 (3):167-171)). In accordance with the invention, a compound and/or composition of the invention is administered to a patient, preferably a human, in need of treatment for a disease which includes but is not limited to, the diseases listed above. Further, in certain embodiments, the compounds and/or compositions of the invention can be administered to a patient, preferably a human, as a preventative measure against diseases or disorders such as those described above. Thus, the compounds and/or compositions of the invention can be administered as a preventative measure to a patient having a predisposition, which includes but is not limited to, the diseases listed above. Accordingly, the compounds and/or compositions of the invention may be used for the prevention of one disease or disorder and concurrently treating another disease *(e.g.,* preventing cancer and treating cardiovascular diseases). It is well within the capability of those of skill in the art to assay and use the compounds and/or compositions of the invention to treat diseases, such as the diseases listed above.

5.10. Therapeutic/Prophylactic Administration

The compounds and/or compositions of the invention may be advantageously

used in medicine, including human medicine. As previously described in Section 5.4 above, compounds and compositions of the invention are useful for the treatment or prevention of diseases, which include but are not limited to, cancers, including, but not limited to, ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, acute lung diseases, including, but not limited to, adult respiratory distress syndrome (ARDS) and acute inflammatory exacerbation of chronic lung diseases such as asthma; surface epithelial cell injury, including, but not limited to, transcomeal freezing or cutaneous bums; cardiovascular diseases, including, but not limited to, ischemia and arthesclerosis.

When used to treat or prevent disease or disorders, compounds and/or compositions of the invention may be administered or applied singly, in combination with other agents. The compounds and/or compositions of the invention may also be administered or applied singly, in combination with other pharmaceutically active agents, including other compounds and/or compositions of the invention.

The current invention provides methods of treatment and prophylaxis by administration to a patient of a therapeutically effective amount of a composition or compound of the invention. The patient may be an animal, is more preferably a mammal, and most preferably a human.

The present compounds and/or compositions of the invention, which comprise one or more compounds of the invention, are preferably administered orally. The compounds and/or compositions of the invention may also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings *(e.g.,* oral mucosa, rectal and intestinal mucosa, *etc.*). Administration can be systemic or local. Various delivery systems are known, *(e.g.,* encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.)* that can be used to administer a compound and/or composition of the invention. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner, and will depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the

compounds and/or compositions of the invention into the bloodstream.

In specific embodiments, it may be desirable to administer one or more compounds and/or composition of the invention locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of the diseases listed above.

In certain embodiments, it may be desirable to introduce one or more compounds and/or compositions of the invention into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

A compound and/or composition of the invention may also be administered directly to the lung by inhalation. For administration by inhalation, a compound and/or composition of the invention may be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, *(e.g.,* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or any other suitable gas) may be used to deliver compounds of the invention directly to the lung.

Alternatively, a Dry Powder Inhaler ("DPI") device may be used to administer a compound and/or composition of the invention to the lung. DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which may then be inhaled by the patient. DPI devices are also well known in the art. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch for these systems.

Another type of device that may be used to deliver a compound and/or a composition of the invention to the lung is a liquid spray device. Liquid spray

systems use extremely small nozzle holes to aerosolize liquid drug formulations that may then be directly inhaled into the lung.

In one embodiment, a nebulizer is used to deliver a compound and/or composition of the invention to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that may be readily inhaled (see *e.g.,* Verschoyle *et al., British J. Cancer* **1999**, 80, Suppl. 2, 96, which is herein incorporated by reference). Examples of nebulizers include devices supplied by Sheffield/Systemic Pulmonary Delivery Ltd. (See, Armer *et al.,* United States Patent No. 5,954,047; van der Linden *et al.,* United States Patent No. 5,950,619; van der Linden *et al.,* United States Patent No. 5,970,974), Aventis and Batelle Pulmonary Therapeutics.

In another embodiment, an electrohydrodynamic ("EHD") aerosol device is used to deliver a compound and/or composition of the invention to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see *e.g.,* Noakes *et al.,* United States Patent No. 4,765,539). EHD aerosol devices may more efficiently deliver drugs to the lung than other pulmonary delivery technologies.

In another embodiment, the compounds of the invention can be delivered in a vesicle, in particular a liposome *(see* Langer, *Science* **1990**, 249:1527-1533; Treat *et al,* in "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); *see* generally "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989)).

In yet another embodiment, the compounds of the invention can be delivered *via* sustained release systems, preferably oral sustained release systems. In one embodiment, a pump may be used *(see* Langer, *supra;* Sefton, 1987, *CRC Crit Ref Biomed. Eng.* 14:201; Saudek *et al., N. Engl. J Med.* **1989**, 321:574).

In another embodiment, polymeric materials can be used *(see* "Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol Sci. Rev. Macromol Chem.* **1983**, 23:61; *see also* Levy *et al., Science* **1985**, 228: 190; Dunng *et al., Ann. Neurol* **1989**, 25:351; Howard *et al., J Neurosurg.* **1989**, 71:105). In a preferred embodiment, polymeric materials are used for oral

sustained release delivery. In another embodiment, enteric-coated preparations can be used for oral sustained release administration. In still another embodiment, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.* **2000**, 26:695-708).

In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds and/or composition of the invention, thus requiring only a fraction of the systemic dose *(see, e.g.* Goodson, in "Medical Applications of Controlled Release," *supra,* vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in Langer, **1990**, *Science* 249:1527-1533 may also be used.

5.11. Compositions of the Invention

The present compositions contain a therapeutically effective amount of one or more compounds of the invention, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide the form for proper administration to a patient. When administered to a patient, the compounds of the invention and pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when the compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

Pharmaceutical compositions comprising a compound of the invention may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries, which facilitate processing of compounds of the invention into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a capsule (see *e.g.,* Grosswald *et al.,* United States Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles have been described in the art (see Remington's Pharmaceutical Sciences, Philadelphia College of Pharmacy and Science, 17th Edition, 1985).

For topical administration compounds of the invention may be formulated as solutions, gels, ointments, creams, suspensions, *etc.* as are well-known in the art.

Systemic formulations include those designed for administration by injection, *e.g.,* subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration. Systemic formulations may be made in combination with a further active agent that improves mucociliary clearance of airway mucus or reduces mucous viscosity. These active agents include, but are not limited to, sodium channel blockers, antibiotics, N-acetyl cysteine, homocysteine and phospholipids.

In a preferred embodiment, the compounds of the invention are formulated in accordance with routine procedures as a composition adapted for intravenous administration to human beings. Typically, compounds of the invention for intravenous administration are solutions in sterile isotonic aqueous buffer. For injection, a compound of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. When necessary, thc compositions may also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. When the compound of the invention is administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. When the compound of the invention is administered by injection, an ampoule of sterile water

for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions may contain one or more optionally agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry coloring agents and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Such vehicles are preferably of pharmaceutical grade.

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkyleneglycols *(e.g.,* propylene glycol), polyalkylene glycols *(e.g.,* polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 *(e.g.,* acetate, citrate, ascorbate at between about 5.0 mM to about 50.0 mM, *etc).* Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines and the like may be added.

For buccal administration, the compositions may take the form of tablets, lozenges, *etc.* formulated in conventional manner.

Liquid drug formulations suitable for use with nebulizers and liquid spray

devices and EHD aerosol devices will typically include a compound of the invention with a pharmaceutically acceptable vehicle. Preferably, the pharmaceutically acceptable vehicle is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds of the invention. Preferably, this material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (see, *e.g.,* Biesalski, United States Patent No. 5,112,598; Biesalski, United States Patent No. 5,556,611).

A compound of the invention may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, *e.g.,* containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, a compound of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation *(e.g.,* subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, a compound of the invention may be formulated with suitable polymeric or hydrophobic materials *(e.g.,* as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

When a compound of the invention is acidic, it may be included in any of the above-described formulations as the free acid, a pharmaceutically acceptable salt, a solvate or hydrate. Pharmaceutically acceptable salts substantially retain the activity of the free acid, may be prepared by reaction with bases and tend to be more soluble in aqueous and other protic solvents than the corresponding free acid form.

5.12. Methods of Use And Doses

A compound of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended purpose. The compounds of the invention or compositions thereof, are administered or applied in a therapeutically effective amount for use to treat or prevent diseases or disorders including but not limited to, ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, acute lung diseases, *(e.g.,* adult respiratory distress syndrome (ARDS) and asthma) surface epithelial cell injury *(e.g.,* transcomeal freezing and cutaneous bums) and cardiovascular diseases such as ischemia and arthesclerosis.

The amount of a compound of the invention that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques known in the art as previously described. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The amount of a compound of the invention administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

For example, the dosage may be delivered in a pharmaceutical composition by a single administration, by multiple applications or controlled release. In a preferred embodiment, the compounds of the invention are delivered by oral sustained release administration. Preferably, in this embodiment, the compounds of the invention are administered twice per day (more preferably, once per day). Dosing may be repeated intermittently, may be provided alone or in combination with other drugs and may continue as long as required for effective treatment of the disease state or disorder.

Suitable dosage ranges for oral administration are dependent on the potency of the, but are generally about 0.001 mg to about 200 mg of a compound of the invention per kilogram body weight. Dosage ranges may be readily determined by methods known to the skilled artisan.

Suitable dosage ranges for intravenous (i.v.) administration are about 0.01 mg to about 100 mg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 mg/kg body weight to about 1 mg/kg body

weight. Suppositories generally contain about 0.01 milligram to about 50 milligrams of a compound of the invention per kilogram body weight and comprise active ingredient in the range of about 0.5% to about 10% by weight. Recommended dosages for intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual or intracerebral administration are in the range of about 0.00 1 mg to about 200 mg per kilogram of body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Animal model systems include, but are not limited to, human tumor xenografts in nude mice. Such animal models and systems are well known in the art (Andersson *et al.*, **2000**, *Acta Oncl.* 39:741-745; Chatzistamou *et al.*, **2001**, *J. Clin. Endocrinol Metab,* 86:2 144-2152).

The compounds of the invention are preferably assayed *in vitro* and *in vivo,* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific compound of the invention or a combination of compounds of the invention is preferred for reducing convulsion. The compounds of the invention may also be demonstrated to be effective and safe using animal model systems.

Preferably, a therapeutically effective dose of a compound of the invention described herein will provide therapeutic benefit without causing substantial toxicity. Toxicity of compounds of the invention may be determined using standard pharmaceutical procedures and may be readily ascertained by the skilled artisan. The dose ratio between toxic and therapeutic effect is the therapeutic index. A compound of the invention will preferably exhibit particularly high therapeutic indices in treating disease and disorders. The dosage of a compound of the inventions described herein will preferably be within a range of circulating concentrations that include an effective dose with little or no toxicity.

5.13. Combination Therapy

In certain embodiments, the compounds of the invention can be used in combination therapy with at least one other therapeutic agent. The compound of the invention and the other therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a compound of the invention is administered concurrently with the administration of another therapeutic agent. In another preferred embodiment, a composition comprising a compound of the

invention is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition as the compound of the invention or a different composition. In another embodiment, a composition comprising a compound of the invention is administered prior or subsequent to administration of another therapeutic agent. Other therapeutic agents, which may be used with the compounds and/or compositions of the invention, include but are not limited to, agonists and antagonists of Edg-2, Edg-3, Edg-4 or Edg-7, drugs used to treat cardiovascular diseases and/or cancer such as, alkylating agents *(e.g.,* cyclophosphamide, melphalan, chlorambucil), platinum compounds *(e.g.*, cisplatin, carboplatin), anthracyclines *(e.g.,* doxorubicin, epirubicin), taxanes *(e.g.,* paclitaxel, docetaxel), chronic oral etoposide, topotecan, gemcitabine, hexamethylamine, methotrexate, and 5-fluorouracil.

5.14. Assays

One of skill in the art can use the following assays to identify Edg-2, Edg-3, Edg-4 or Edg-7 agonists or antagonists.

5.14.1. Intracellular Calcium Measurement Assays

Specific assays for Edg-2, Edg-3, Edg-4 or Edg-7 receptor activity are known to those of skill in the art. For example, cells expressing Edg-2, Edg-3, Edg-4 or Edg-7 receptors can be contacted with a membrane-permeant calcium sensitive dye such as Fluo-4 AM or a proprietary calcium dye loading kit *(e.g.*, FLIPR Calcium Assay kit, Molecular Devices, Sunnyvale, CA). Intracellular calcium is capable of binding to the dye and emitting fluorescent radiation when illuminated at the appropriate wavelength. The cells can thus be illuminated an appropriate wavelength for the dye and any emitting light can be captured by a cooled CCD camera. Changes in fluorescence indicate changes in intracellular calcium resulting from the activation of an Edg-2, Edg-3, Edg-4 or Edg-7 receptor. Such changes can be measured advantageously in whole cells in "real-time" (Berridge *et al.*, Nature Reviews **2000**, 1:11-21).

Other methods of measuring intracellular calcium are known to those of skill in the art. For instance, a commonly used technique is the expression of receptors of interest in *Xenopus laevis* oocytes followed by measurement of calcium activated

chloride currents (see Weber, 1999, *Biochim Biophys Acta* 142 1:213-233). In addition, several calcium sensitive dyes are available for the measurement of intracellular calcium. Such dyes can be membrane permeant or not membrane permeant. Examples of useful membrane permeant dyes include acetoxymethyl ester forms of dyes that can be cleaved by intracellular esterases to form a free acid, which is no longer membrane permeant and remains trapped inside a cell. Dyes that are not membrane permeant can be introduced into the cell by microinjection, chemical permeabilization, scrape loading and similar techniques (Haughland, 1993, in "Fluorescent and Luminescent Probes for Biological Activity" ed. Mason, W.T. pp 34-43; Academic Press, London; Haughland, 1996, in "Handbook of Fluorescent Probes and Research Chemicals", sixth edition, Molecular Probes, Eugene, OR).

5.14.2. IL-8 and VEGF Assays

The levels of interleukin-8 ("IL-8") and vascular endothelial growth factor ("VEGF") are important markers for the proliferative potential, angiogenic capacity and metastatic potential of a tumor cell line. Specific assays for IL-8 and VEGF are known to those of skill in the art. For example, IL-8 and VEGF assays can be performed by techniques that include, but are not limited to, a standard enzyme-linked inimunosorbent assay ("ELISA"). In a standard ELISA, the cells can be cultured, for example, in a 96 well format, serum starved overnight, and treated with LPA or S1P. Dose ranges would be known to one of skill in the art. For example, the doses can range from 0.1-10 μM in serum free medium. Cell supernatants can then be collected to measure the amount of IL-8 or VEGF secreted.

Methods to measure the amount of IL-8 or VEGF secreted are known to one of skill in the art. In one method, an anti-IL-8 or anti-VEGF capture antibody can be adsorbed on to any surface, for example, a plastic dish. Cell supernatants containing IL-8or VEGF can then be added to the dish and any method known in the art for detecting antibodies can be used to detect the anti-IEIL-8 or anti-VEGF antibody. In one embodiment, an anti-IL-8 or anti-VEGF biotinylated detection antibody and streptavidin-HRP can be used for detection via the addition of a substrate solution and colorimetric reading using a microtiter plate reader. The level of IL-8 or VEGF can be interpolated by non-linear regression analysis from a standard curve.

5.14.3. Migration and Invasion Assays

Migration and invasion assays are known to one of skill in the art. For example, migration assays can be designed to measure the chemotactic potential of the cell line, or its movement toward a concentration gradient of chemoattractants, such as, but not limited to, LPA or S1P. Invasion assays can be designed, for example, to evaluate the ability of the cell line to pass through a basement membrane, a key feature of metastasis formation.

Specific assays, known to one of skill in the art include a modified Boyden Chamber assay in which a cell suspension can be prepared in serum free medium and added to the top chamber. The concentration of cells to be added, for example, about 10^5 cells/ml is known to one of skill in the art. An appropriate dose of a chemoattractant can then be added to the bottom chamber. Following an incubation period, the number of cells invading the lower chamber can be quantified by methods known in the art. In one embodiment, Fluoroblok filter inserts can be used and the number of cells migrating to the lower chamber can be quantified by staining the filter inserts and detecting the fluorescence by any means known in the art. The level of fluorescence may be correlated with the number of migrating cells.

5.14.4. Proliferation Assay

Proliferation assays quantitate the extent of cellular proliferation in response to a stimulant, which, in the case of Edg-2, Edg-3, Edg-4 or Edg-7 receptors, may be LPA or S1P. Cells can be plated and treated with the stimulant *(e.g.,* LPA or S1P) with or without any serum starvation. Stimulant doses may range from 0.1 to 10 μM and in any event may be readily determined by those of skill in the art. Typically, the cells can be treated for a period of a few hours to a few days before cellular proliferation is measured.

Specific methods to determine the extent of cell proliferation are known to one of skill in the art. For example, one method is bioluminescent measurement of ATP, which is present in all metabolically active cells. ATP can be extracted by addition of Nucleotide Releasing Reagent and its release can be monitored by the addition of the ATP Monitoring Reagent. An enzyme, such as luciferase, which catalyzes the formation of light from ATP and luciferin, can be used to quantitate the amount of ATP present.

5.14.5. Cyclic AMP Assay

Because cAMP acts a second messenger in cell signaling, activating protein kinases that in turn phosphorylate enzymes and transcription factors, cAMP concentration is frequently indicative of the activation state of downstream signaling pathways. For GPCRs like the Edg receptors, coupling via a Gui pathway results in inhibition of adenylyl cyclase activity, the key enzyme involved in breakdown of ATP and formation of cAMP. Thus, assays can be designed to measure inhibition of adenylyl cyclase activity, by first stimulating cAMP formation. One example of a compound, which stimulates cAMP formation is forskolin. Forskolin bypasses the receptor and directly activates adenylyl cyclase. Under these conditions, activation of a Gαi coupled receptor will inhibit forskolin-stimulated cAMP, and an antagonist at such a receptor will reverse the inhibition.

This assay can be performed by any means known to one of skill in the art. For example, cells can be plated and treated with or without any serum starvation. The cells may be initially treated with a compound, such as forskolin, to induce cAMP production. This is followed by the addition of an Edg-2, Edg-3, Edg-4 or Edg-7 stimulator, for example, LPA or S1P. The dose of stimulator required is well known in the art, and could be in the range from 0.1-10 αM in serum free medium. Following an incubation period, the cells are lysed and the level of cAMP is determined.

The cAMP assay can be performed by any means known to one of skill in the art, for example, by performing a competitive immunoassay. Cell lysates can be added to a plate precoated with anti-cAMP antibody, along with a cAMP-AP conjugate and a secondary anti-cAMP antibody. Detection can be performed by any appropriate means, including, but not limited to, using a substrate solution and chemiluminescent readout.

6. EXAMPLES

The invention is further defined by reference to the following examples, which describe in detail preparation of compounds and compositions of the invention and assays for using compounds and compositions of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

6.1. Example 1: Synthesis of 4,4,4-trifluoro-3-oxo-*N*-(5-phenyl-2H-pyrazol-3-yl)-butyramide (101)

Ethyl 4,4,4-trifluoroacetoacetate (3.45 mL, 23.6 mmol) and acetic acid (5.2 mL) were added to 5-phenyl-1H-pyrazol-3-ylamine (2.5 g, 15.7 mmol). The reaction mixture was heated for 2.5 hours at 120°C, cooled to room temperature, concentrated *in vacuo* and purified by flash chromatography on silica gel (chloroform/methanol/concentrated aqueous animonium hydroxide) to provide 3.35 g (72% yield) of **101** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.8 (s, 1H), 10.6 (s, 1H), 7.85 (m, 2H), 7.30 (m, 3H), 6.92 (s, 1H), 3.04 (m, 1H), 2.72 (m, 1H). APCI-MS: m/z = 298 [$C_{13}H_{,10}F_3N_3O_2$+ H]. Melting range: 318.6-321.1°C (decomposed).

6.2. Example 2: Synthesis of *N*-[5-(3,4-dichloro-phenyl)-2H-pyrazol-3-yl]-4,4,4-trifluoro-3-oxo-butyramide (103)

Thiosemicarbazide (1.15 g, 12.6 mmol) was added to 3', 4'-dichloroacetophenone (2.0 g, 10.6 mmol) in acetic acid (.12 mL) and ethanol (21 mL) (Dimmock *et al.*, **1991**, *Eur. J. Med. Chem.* 26:529). The reaction mixture was stirred for 4 days at room temperature, concentrated *in vacuo* and the resultant oil was taken up in chloroform. The chloroform solution was washed successively with saturated aqueous sodium bicarbonate, water and brine, dried with sodium sulfate and concentrated *in vacuo* to give 2.47 g (89%) of the thiosemicarbazone as a white solid. ^{1}H NIMIR (DMS0-*d6*) δ: 9.7 (br, 1H), 8.37 (s, 1H), 8.28 (m, 1H), 8.22 (s, 1H), 7.89 (m, 1H), 7.13 (m, 1H), 2.24 (s, 3H).

The thiosemicarbazone of 3',4'-dichloroacetophenone (2.5g, 9.43 mmol) was added to a solution of lithium diisopropylamide (39.6 nimol) in THF (20 mL) at 0 °C (Beam, *et al.*, **1997**, *J. Heterocyclic Chem.* 34:1549). After two hours at 0 °C, aqueous hydrochloric acid (63 mL, 3N) was added and the reaction mixture was heated for 1 hour at 100 °C, poured into ice water (200 mL) and neutralized with solid sodium bicarbonate. Extraction of the aqueous mixture with chloroform followed by flash column chromatography on silica gel (4-7% methanol in methylene chloride) provided 1.55 g (72%) of 5-(3,4-dichloro-phenyl)-1H-pyrazol-3-ylamine as a tan foam. ^{1}H NMR (300 MHz, DMS0-d_6) δ: 11.8 (br, lH), 7.8 (s, 1H), 7.6 (m, 2H), 5.8 (s, 1H), 4.8 (br, 2H). CI-MS: m/z = 228 [$C_9H_7C1_2N_3$ + H].

Finally, following the procedure of Example 1, 5-(3,4-dichloro-phenyl)-1H-

pyrazol-3-ylamine (0.25 g, 1.10 mmol) was reacted with ethyl 4,4,4-trifluoroacetoacetate (0.16 mL, 1.10 mmol) to provide 67 mg (17%) of **103** as a white solid. ^{1}H NMR (300 MHz, DMS0-d_6) δ: 13.07 (s, 1H), 10.78 (s, 1H), 8.23 (s, IH), 7.88 (m, 1H), 7.76 (m, 1H), 7.27 (s, 1H), 3.06 (m, 1H), 2.77 (m, 1H). CI-MS: m/z = 366 [$C_{13}H_8C1_2F_3N_302$+ H].

6.3. Example 3: Synthesis of 4,4-4-trifluoro-*N*-[5-(4-methoxy-phenyl)-2-pyrazol-3-yl]-3-oxo-butyramide (105)

Following the procedure of Example 1, 5-(4-methoxy-phenyl)-2H-pyrazol-3-ylamine (0.20 g, 1.05 mmol) (Beam, *et al.*, **1997,** *J. Heterocyclic Chem.* 34:1549; Grandin, **1971**, *Bull. Chim. Soc. Fr.* 4002) was reacted with ethyl 4,4,4-trifluoroacetoacetate (0.23 mL, 1.60 mmol) to provide 177mg (51%) of **105** as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.62 (s, 1H), 10.57 (s, 1H), 7.77 (m, 2H), 6.92 (m, 3H), 3.70 (s, 3H), 2.93 (m, 1H), 2.68 (m, 1H). APCI-MS: m/z = 328 [$C_{14}H_{12}F_3N_3O_3$ + H]. Melting Range: 307-310 °C (decomposed).

6.4. Example 4: Synthesis of 4,4-4-trifluoro-*N*-15-(4-fluoro-phenyl)2H-pyrazol 3-yl]-3-oxo-butyramide (107)

Following the procedure of Example 1, 5-(4-fluoro-phenyl)-2H-pyrazol-3-ylamine (0.30 g, 1.69 mmol) (Beam, *et al.*, **1997,** *J. Heterocyclic Chem.* 34:1549; Joshi *et al.*, **1979,** *J. Heterocyclic Chem.* 16:1141) was reacted with ethyl 4,4,4-trifluoroacetoacetate (0.37 mL, 2.54 mmol) to provide 205 mg (39%) of **107** as a white solid. ^{1}H NMR (300 MHz, DM50-d_6) δ: 12.78 (s, 1H), 10.62 (s, 1H), 7.83 (m, 2H), 7.32 (m, 2H), 6.96 (s, 1H), 2.93 (m, 1H), 2.70 (m, 1H). APCI-MS: m/z = 316 [$C_{13}H_9F_4N_3O_2$ + H]. Melting Range: 308-310 °C (decomposed).

6.5. Example 5: synthesis of 2-chloro-4,4,4-trifluoro-3-oxo-*N*-(5-phenyl-2H-pyrazol-3-yl)-butyramide (109)

Following the procedure of Example 1, 5-phenyl-1H-pyrazol-3-ylamine (0.25 g, 1.57 mmol) was reacted with ethyl 2-chloro-3-keto-4,4,4-trifluorobutyrate (515 mg, 2.36 mmol) to provide 219 mg (42%) of **109** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.95 (s, 1H), 11.03 (s, 1H), 7.77 (m, 2H), 5.39 (m, 4H), 4.42 (s, 1H). CI-MS: m/z = 332 [C13H_9C1$F_3N_3O_2$ + H]. Melting Range: 259-261 °C (decomposed).

6.6. Example 6: Synthesis of N-[5-(3,5-dimethoxy-phenyl)-2H-pyrazol-3-yl]-4,4,4-trifluoro-3-oxo-butyramide (111)

Thiosemicarbazide (1.9 g, 20.8 mmol) was added to 3', 5'-dimethoxyacetophenone (2.5 g, 13.9 mmol) following the procedure of Example 2 to give 3.5 g (100%) of the thiosemicarbazone as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.2 (s, 1H), 8.3 (s, 1H), 7.9 (s, 1H), 7.0 (s, 2H), 6.5 (s, 1H), 3.7 (s, 6H), 2.3 (s, 3H).

The thiosemicarbazone of 3',5'-dimethoxyacetophenone (3.5 g, 13.9 mmol) was reacted with base following the procedure of Example 2, to give 2.3 g (75%) of 5-(3,5-dimethoxy-phenyl)-2H-pyrazol-3-ylamine (Beam, *et al.*, **1997,** *J. Heterocyclic Chem.* 34:1549). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.9 (br, 1H), 6.8 (s, 2H), 6.4 (s, 1H), 5.8 (m, 1H), 4.7 (br, 2H), 3.8 (s, 6H).

Finally, following the procedure of Example 1, reaction of 5-(3,5-dimethoxy-phenyl)-2H-pyrazol-3-ylamine (0.30 g, 1.37 mmol) with ethyl 4,4,4-trifluoroacetoacetate (0.30 mL, 2.05 mmol) provided 261 mg (53%) of **111** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 6: 12.83 (s, 1H), 10.78 (s, 1H), 7.14 (s, 2H), 7.08 (s, 1H), 6.52 (s, 1H), 3.77 (s, 6H), 2.99 (m, 1H), 2.78 (m, 1H). APCI-MS: m/z = 358 [$C_{15}H_{14}F_3N_3O_4$ + H]. Melting Range: 119-121 °C.

6.7. Example 7: Synthesis of 4,4,4-trifluoro-N-[5-(3-methoxy-phenyl)-2H-pyrazol-3-yl]-3-oxo-butyramide (113)

Following the procedure of Example 1, 5-(3-methoxy-phenyl)-2H-pyrazol-3-ylamine (0.32 g, 1.70 mmol) (Beam *et al,* **1997,** *J. Heterocyclic Chem.* 34:1549; Bruni *et al.*, **1993,** *J. Pharm. Sci.* 82:480) was reacted with ethyl 4,4,4-trifluoroacetoacetate (0.37 mL, 2.54 mmol) to provide 183 mg (33%) of 113 as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.81 (s, 1H), 10.68 (s, 1H), 7.54 (s, 1H), 7.42(m, 2H), 7.06 (s, 1H), 6.96 (m, 1H), 3.78 (s, 3H), 2.98 (m, 1H), 2.76 (m, 1H). APCI-MS: m/z = 328 [$C_{14}H_{12}F_3N_3O_3$ + H]. Melting Range: 107-110 °C.

6.8. Example 8: Synthesis of *N*-(5-benzo[3]dioxol-5-yl-2H-pyrazol-3-yl)-4,4,4-trifluoro-3-oxo-butyramide (115)

The thiosemicarbazone of 3',4'-(methylenedioxy) acetophenone (2.6 g, 11.1 mmol) was prepared following the procedure of Example 2 (Dimmock *et al.*, **1991,**

Eur. J. Med. Chem. 26:529). Reaction of the thiosemicarbazone with base following the procedure of Example 2 provided 0.37 g (16%) of 5-benzo[1,3]dioxol-5-yl-2H-pyrazol-3-ylamine as an orange foam (Beam, *et al.*, **1997,** *J. Heterocyclic Chem.* 34:1549). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.7 (br, 1H), 7.2 (s, 1H), 7.0 (m, 2H), 6.0 (s, 2H), 5.7 (s, 1H), 4.7 (br, 2H). C1-MS m/z 204 [$C_{10}H_9N_3O_2$ + H].

Then following the procedure of Example 1, 5-benzo[1,3]dioxol-5-yl-2H-pyrazol-3-ylamine (0.36 g, 1.77 mmol) was reacted with ethyl 4,4,4-trifluoroacetoacetate (0.39 mL, 2.66 mmol) to provide 164mg (27%) of **115** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.69 (s, 1H), 10.67 (s, 1H), 7.48 (s, 1H), 7.36 (m, 1H), 7.02 (m, 2H), 6.09 (s, 2H), 2.96 (m, 1H), 2.77 (m, 1H). APCI-MS: m/z = 342 [$C_{14}H_{10}F_3N_3O_4$ + H]. Melting Range: 128-130 °C.

6.9. Example 9: Synthesis of 4,4,4-trifluoro-2-methyl-3-oxo-N-[5-phenyl-2H-pyrazol-3-yl]-butyramide (117)

Following the procedure of Example 1, 5-phenyl-IH-pyrazol-3-ylamine (0.25 g, 1.57 mmol) was reacted with ethyl 2-methyl-4,4,4-trifluoroacetoacetate (0.47, 2.36 mmol) to provide 75 mg (15%) of **117** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 6: 12.67 (s, 1H), 10.51 (s, 1H), 7.78 (m, 2H), 7.41 (m, 3H), 6.58 (s, 1H), 2.64 (m, 1H), 1.15 (m, 3H). CI-MS: m/z = 312 [$C_{14}H_{12}F_3N_3O_2$ + H]. Melting Range: 286-288 °C (decomposed).

6.10. Example 10: Synthesis of 3-phenyl-5-(4,4,4-trifluoro-3-oxo-butyrylamino)-pyrazole-1-carboxylic acid allylamide (119)

4,4,4-trifluoro-3-oxo-N-(5-phenyl-2H-pyrazol-3-yl)-butyramide (**101**) was reacted with allyl isocyanate (0.09 mL, 1.0 mmol) in DMF (1 mL) at room temperature for 3 hours. Concentration *in vacuo* and purification by flash column chromatography on silica (chloroform/methanol/concentrated aqueous ammonium hydroxide) provided 190 mg (98%) of **119** as a white solid. ^{1}H NMR (390 MHz, DMSO-d_6) δ: 9.87 (s, 1H), 8.89 (m, IH), 8.12 (m, 2H), 7.43 (m, 3H), 7.32 (s, IH), 5.88 (m, 1H), 5.13 (m, 2H), 3.87 (m, 2H), 3.22 (m, IH), 2.91 (m, IH). CI-MS: m/z= 381 [$C_{,7}H_{,5}F_3N_4O_3$ + H]. Melting Range: 114-116 °C.

6.11. Example 11: Synthesis of N-[5-(2-Bromophenyl)-2H-pyrazole-3-yl]-4,4,4-trifluoro-3-oxo-butyramide (133)

A mixture of 2-bromoacetophenone (2 ml, 14 mmol), thiosemicarbazide (2g, 22 mmol), acetic acid (0.17 ml) and methanol (29 ml) was stirred for 16.5 hours at room temperature. The mixture was concentrated *in vacuo* to obtain 2-bromoacetophenone thiosemicarbazone (3.39 g, 85%). 2-bromoacetophenone thiosemicarbazone was identified by NMR and was used without further purification.

Next, a solution of 2-bromoacetophenone thiosemicarbazone (3.39 g, 12.5 mmol) in tetrahydrofuran (63 ml) was added drop-wise to lithium diisopropylamide (2M in tetrahydrofuran, 37.3 ml, 74.6 mmol) at 0°C under nitrogen atmosphere. After the reaction was completed (as analyzed by TLC), the mixture was quenched with hydrochloric acid (3N, 83 ml), and the organic layer was dried and concentrated *in vacuo*. Following a silica gel chromatography (5-7.5 % methanol/dichloromethane), 3-amino-5-(2'-bromophenyl)-2H-pyrazole (0.688 g, 23 %) was obtained as a brown oil and identified by NMR.

Then a mixture of 3-amino-5-(2'-bromophenyl)-2H-pyrazole (0.68 g, 2.86 mmol), ethyl-4,4,4-trifluoroacetoacetate (0.63 ml, 4.29 mmol) and acetic acid (1 ml) was stirred at reflux for 1.5 hours, then cooled to room temperature and concentrated *in vacuo*. The residue was azeotroped with toluene (70 ml) and the crude product was chromatographed twice on silica gel (20-40 % CMA/dichloromethane; CMA = 80:18:2 chloroform:methanol:ammonium hydroxide). A tan solid **133** (0.264 g, 25 %) was obtained: mp 128-131°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ. 12.68 (s, 1H), 10.72 (s, 1H), 7.73 (d, 1H), 7.54 (d, 1H), 7.41 (m, 1H), 6.55 (s, 2H), 2.83 (q, 2H); APCI MS m/z 376 $[C_{13}H_9BrF_3N_3O_2 + H]^+$.

6.12. Example 12: Synthesis of N-[5-(2',4'-dimethoxyphenyl)-2H-pyrazole-3-yl]-4,4,4-trifluoro-3-oxo-butyramide (135)

A mixture of 2,4-dimethoxyacetophenone (2.5 g, 13.9 mmol), thiosemicarbazide (1.9 g, 20.8 mmol), acetic acid (0.159 ml) and methanol (28 ml) was heated for five days with stirring. The mixture was cooled to room temperature and concentrated *in vacuo* to obtain 2,4-dimethoxyacetophenone thiosemicarbazone (4.29 g, >100%) as a tan solid. 2,4-dimethoxyacetophenone thiosemicarbazone was identified by NMR and was used without further purification.

Next, a solution of 2,4-dimethoxyacetophenone thiosemicarbazone (4.29 g, 16.9 mmol) in tetrahydrofuran (85 ml) was added drop-wise to lithium

diisopropylamide (2M in tetrahydrofuran, 59 ml, 199 mmol) at ambient temperature under nitrogen atmosphere. After the reaction was completed (as analyzed by TLC), the mixture was quenched with hydrochloric acid (4N, 113 ml), and the organic layer was dried and concentrated *in vacuo*. Following a silica gel chromatography (5-7.5 % methanol/dichloromethane), 3-amino-5-(2',4'-dimethoxyphenyl)-2H-pyrazole (2.36 g, 64 %) was obtained as a yellow-brown solid and identified by NMR.

Then a mixture of 3-amino-5-(2',4'-dimethoxyphenyl)-2H-pyrazole (0.3 g, 1.37 mmol) , ethyl-4,4,4-trifluoroacetoacetate (0.3 ml, 2.05 mmol) and acetic acid (0.5 ml) was stirred at reflux for 1.75 hours, then cooled to room temperature and concentrated *in vacuo*. The residue was azeotroped with toluene (70 ml) and the resulting residue was chromatographed on silica gel (20-40 % CMA/dichloromethane; CMA = 80:18:2 chloroform:methanol:ammonium hydroxide), followed by a second silica gel chromatography (30-45 % methanol/dichloromethane). A white solid **135** (0.245 g, 50 %) was obtained: mp 125-128°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.35 (s, 1H), 10.61 (s, 1H), 7.46 (d, 1H), 6.65 (s, 1H), 6.58 (d, 1H), 6.45 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.81 (q, 2H); CI MS m/z 358 $[C_{15}H_{14}F_3N_3O_4 + H]^+$.

6.13. Example 13: Synthesis of 4,4,4-trifluoro-3-oxo-N-(5-thiophen-2-yl-2H-pyrazol-3-yl)butyramide (137)

A mixture of 2-amino-5-(2'-thienyl)-2H-pyrazole (0.25 g, 1.52 mmol), ethyl-4,4,4-trifluoroacetoacetate (0.332 ml, 2.28 mmol) and acetic acid (0.5 ml) was stirred at reflux for 1.5 hours and cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (20-40 % CMA/dichloromethane; CMA = 80:18:2 chloroform:methanol:ammonium hydroxide). A white solid **137** (0.332 g, 72 %) was obtained: mp 259-261°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (bs, 1H), 10.78 (bs, 1H), 7.75 (d, 2H), 7.15 (s, 1H), 7.08 (s, 1H), 3.01 (d, 1H), 2.78 (d, 1H); CI MS m/z 304 $[C_{11}H_8F_3N_3O_2S + H]^+$.

6.14. Example 14: Synthesis of 4,4,4-trifluoro-3-oxo-N-(5-thiophen-3-yl-2H-pyrazol-3-yl)butyramide (139)

A mixture of 3-acetylthiophene (2.5 g, 19.8 mmol), thiosemicarbazide (2.7 g, 29.7 mmol), acetic acid (0.226 ml) and methanol (40 ml) was stirred at 70°C for 14 hours and cooled to room temperature. The mixture was concentrated *in vacuo*, and 3-acetylthiophene thiosemicarbazone (3.92 g, 100 %) was obtained as a pale yellow

solid. The compound was identified by NMR.

Next, a solution of 3-acetylthiophene thiosemicarbazone (2 g, 10.1 mmol) in tetrahydrofuran (50 ml) was added drop-wise to lithium diisopropylamide (2M in tetrahydrofuran, 30 ml, 60 mmol) at 0°C under nitrogen atmosphere. After the reaction was completed (as analyzed by TLC), the mixture was qhenched with hydrochloric acid (3N, 67 ml), and the organic layer was dried using magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (4-8 % methanol/dichloromethane), and 3-amino-5-(3-thienyl)-2H-pyrazole (1 g, 60%) was obtained as a brown oil. The compound was identified by NMR.

Then a mixture of 3-amino-5-(3-thienyl)-2H-pyrazole (0.9 g, 5.45 mmol), ethyl-4,4,4-trifluoroacetoacetate (1.2 ml, 8.2 mmol) and acetic acid (2 ml) was stirred for 1.5 hours at reflux, and then cooled to room temperature. The mixture was concentrated *in vacuo* and azeotroped with toluene. The residue was chromatographed on silica gel (20-60 % CMA/dichloromethane; CMA = 80:18:2 chloroform:methanol:ammonium hydroxide). A tan solid **139** (0.119 g, 7.2 %) was obtained: mp 251-253°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H), 10.61 (s, 1H), 8.19 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.12 (s, 1H), 3.01 (d, 1H), 2.79 (d, 1H); CI MS m/z 304 $[C_{11}H_8F_3N_3O_2S + H]^+$.

6.15. Example 15: Synthesis of 4,4,4-trifluoro-3-oxo-N-(5-pyridin-4-yl-2H-pyrazol-3-yl)butyramide (141)

Hydrazine (0.6 ml, 19 mmol) was added to a mixture of cyanoacetyl-4-pyridine (1.39 g, 9.52 mmol) in acetic acid (6 ml). The addition resulted in an exotherm and the mixture was heated for 2.5 hours. The mixture was then cooled to room temperature and diluted with 37 ml of water. Concentrated hydrochloric acid (0.16 ml) was added, and the mixture was heated for 0.5 hour. The mixture was again cooled to room temperature and filtered. N-(5-pyridin-4-yl-2H-pyrazol-3-yl)acetamide (1 g, 50 %) was obtained as an orange solid. The compound was identified by NMR and mass spectral analyses.

Next, a mixture of N-(5-pyridin-4-yl-2H-pyrazol-3-yl)acetamide (1 g, 4.95 mmol) and hydrochloric acid (1N, 20 ml) was heated for 4 hours, and then cooled to room temperature and filtered with water wash. The filtrate was neutralized with

saturated sodium bicarbonate and extracted three times with methylene chloride. The combined extracts were dired using sodium sulfate and concentrated *in vacuo*. 3-amino-5-(4-pyridyl)-2H-pyrazole (0.122 g, 15 %) was obtained as a yellow solid. The compound was identified by NMR.

Then a mixture of 3-amino-5-(4-pyridyl)-2H-pyrazole (0.122 g, 0.76 mmol), ethyl-4,4,4-trifluoroacetoacetate (0.167 ml, 1.14 mmol) and acetic acid (0.5 ml) was stirred at reflux for 1.5 hours and then cooled to room temperature. The mixture was diluted with toluene and concentrated *in vacuo*. The residue was chromatographed twice on silica gel (25-75 % CMA/dichloromethane then 40 % CMA/dichloromethane; CMA = 80:18:2 chloroform:methanol:ammonium hydroxide). A yellow solid **141** (48.8 mg, 21.6 %) was obtained: mp 364-366°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.13 (s, 1H), 10.76 (s, 1H), 8.69 (s, 2H), 7.98 (s, 2H), 7.25 (s, 1H), 3.17 (d, 1H), 2.80 (d, 1H); CI MS m/z 299 $[C_{12}H_9F_3N_4O_2 + H]^+$.

6.16. Example 16: Synthesis of 5-p-Tolyl-1H-imidazole-2-thiol (143)

2-oxo-2-p-tolyl-ethylammonium chloride was prepared according to the procedures described in *Synthesis*, pp. 615-618 (1990). Starting from 2-bromo-4'-methylacetophenone (Aldrich), a substitution reaction by sodium diformylamide (TCI-US), followed by an acidic hydrolysis, was performed to provide 95 % yield.

2-oxo-2-p-tolyl-ethylammonium chloride (37.74 g, 0.203 mol), KSCN (Acros, 21.84 g, 0.225 mol, 1.1 equivalent) in glacial acetic acid (500 ml) were stirred at 120-125°C (oil bath temperature) for 2 hours (*J. Ind. Chem. Soc.*, 58:1117-1118 (1981)). The content was then cooled to room temperature, and water (500 ml) was added. The mixture was chilled with an ice bath for 1 hour. The solid product was collected by suction filtration, washed with water, and air-dried. 5-p-tolyl-1H-immidazole-2-thiol was obtained as a yellow solid (37.17 g, 96 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.47 (s, 1H), 12.10 (s, 1H), 7.56 (m, 2H), 7.32 (s, 1H), 7.18 (m, 2H), 2.29 (s, 3H); APCI-MS m/z 191 $[C_{10}H_{10}N_2S + H]^+$; m.p. 266-267°C.

6.17. Example 17: Synthesis of 5-(1H-Indol-3-yl)-6-phenyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (121)

Compound **121** was synthesized using the procedures disclosed in Russ, *J. Org. Chem.* 36: 626-628 (200). A mixture of the 6-phenyl-1,2,4-triazin(2H)one

(0.097 g, 0.56 mmol), indole (0.066 g, 0.56 mmol) and acetic acid (2 ml) was stirred at reflux for 12 hours. The acetic acid was removed *in vacuo*. Water (10 ml) was added to form a white precipitate, and the precipitate was filtered and washed with water. Recrystallization from methanol provided 5-(1H-Indol-3-yl)-6-phenyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (0.14 g, 86%) as a white solid: mp 281 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (t, 3H), 7.32 (d, 1H), 7.28 (d, 3H), 7.19 (s, 1H), 7.10 (t, 1H), 7.05 (t, 1H), 6.02 (s, 1H); ESI MS m/z 291 $[C_{17}H_{14}N_4O+H]^+$.

6.18. Example 18: Resolution of (+) and (-) Isomers of 5-(1H-Indol-3-yl)-6-phenyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (121)

The (+) and (-) isomers of compound 121 were resolved by a chromatographic method. The chromatography was done using Chiralpak AD 50x500 mm column and 60:40 2-propanol/hexane at a flow rate of 118 ml/min.

(+)-5-(1H-Indol-3-yl)-6-phenyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (0.043 g, $[\alpha]^{25}_D$ +78.5° (c 0.169, THF)) was recovered as a white solid: mp 281°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (t, 3H), 7.35 (d, 1H), 7.29 (s, 3H), 7.20 (s, 1H), 7.11 (t, 1H), 7.05 (t, 1H), 6.03 (s, 1H); ESI MS m/z 291 $[C_{17}H_{14}N_4O+H]^+$.

(-)-5-(1H-Indol-3-yl)-6-phenyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (0.038 g, $[\alpha]^{25}_D$ –71.5° (c 0.186, THF)) was also recovered from the same chromatography as a white solid: mp 281°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (m, 3H), 7.36 (d, 1H), 7.28 (s, 3H), 7.21 (s, 1H), 7.16 (t, 1H), 7.09 (t, 1H), 6.04 (s, 1H); ESI MS m/z 291 $[C_{17}H_{14}N_4O+H]^+$.

6.19 Example 19: Synthesis of 1-(2,6-dichlorophenyl)-6,7-dimethoxy-1,4-dihydro-2H-isoquinolin-3-one

3,4-Dimethoxyphenyl acetonitrile (3.54 g, 20 mmol) was added to polyphosphoric acid (11.1 g) preheated to 130°C. After 1 hour, 2,6-dichlorobenzaldehyde (1.75 g, 20 mmol) was added. The resulting mixture was stirred for 12 hours and cooled to ambient temperature. Following an addition of water (50 ml), concentrated ammonium hydroxide was added. The mixture was allowed to stand for 18 hours. The solids were filtered, then stirred at reflux in sodium hydroxide (1.35 M, 50 ml) for 2 hours. The mixture was filtered while hot, and the solid was washed with water and dried. The solid was chromatographed (silica gel, 5 to 50 % ethyl acetate/dichloromethane) to provide 1-(2,6-

dichlorophenyl)-6,7-dimethoxy-1,4-dihydro-2H-isoquinolin-3-one (0.305 g, 9 %) as a slightly yellow solid: m.p. 228-229°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (bs, 2H), 7.36 (t, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 6.38 (s, 1H), 3.87 (s, 3H), 3.69 (d, 2H), 3.62 (s, 3H); ESI-MS m/z 352 $[C_{17}H_{15}C_{12}NO_3 + H]^+$.

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6.20 Example 20: Synthesis of 3-(2-chloro-6-fluorophenyl)-6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine (127)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 1.32 g, 6.91 mmol), 4-methylmorpholine (0.76 ml, 6.91 mmol), 1-hydroxybenzotriazole hydrate (HOBt, 0.132 g, 0.98 mmol) and 5-trifluoromethylpyridyl hydrazine (68%, 1.5 g, 5.76 mmol) were added to 2-chloro-6-fluorobenzoic acid (1.0 g, 5.76 mmol) in anhydrous 1:1 dichloromethane/acetonitrile (40 ml) at 0 °C. The ice bath was removed and the mixture was stirred at ambient temperature for 60 hours. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (120 ml), washed with water (three times, 30 ml each) and brine (40 ml), dried with magnesium sulfate, and concentrated *in vacuo*. Following a flash silica gel chromatography (5-33% ethyl acetate/dichloromethane), 2-chloro-6-fluorobenzoic acid-N-(5-trifluoromethylpyridin-2-yl)hydrazide (0.542 g, 28%) was obtained as a green solid. The compound was identified by NMR spectral analysis.

Next, phosphorous oxychloride (3.0 ml, 32.4 mmol) was added to a solution of 2-chloro-6-fluorobenzoic acid-N-(5-trifluoromethyl-pyridin-2-yl)hydrazide (0.542 g, 1.62 mmol) in anhydrous toluene (40 ml). The mixture was stirred at reflux for 18 hours. The mixture was then poured into cold sodium hydroxide (2M, 100ml), extracted with ethyl acetate, washed with water (35 ml) and brine (35 ml), dried with magnesium sulfate. Extra solvent was removed *in vacuo*. Following a flash silica gel chromatography (5-50% ethyl acetate/dichloromethane), 3-(2-chloro-6-fluorophenyl)-6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine **127** (0.117 g, 23%) was obtained as a light yellow solid: mp 170-171°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.60 (s, 1H), 8.10 (d, 1H), 7.80 (m, 2H), 7.65 (d, 1H), 7.45 (t, 1H); ESI MS m/z 316 $[C_{13}H_6ClF_4N_3 + H]^+$.

6.21 Example 21: Synthesis of 3-(2,3-dichlorophenyl)-6-trifluoromethyl [1,2,4]triazolo[4,3-a]pyridine (129)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 1.325 g, 6.91 mmol), N-methylmorpholine (0.76 ml, 6.91 mmol), 1-hydroxybenzotriazole hydrate (HOBt, 0.177 g, 1.31 mmol) and -trifluoromethylpyridyl hydrazine (68%, 1.0 g, 3.84 mmol) were added to 2,3-dichlorobenzoic acid (1.0 g, 5.76 mmol)in anhydrous 1:1 dichloromethane/acetonitrile (40 ml) at 0°C. The ice bath was removed and the mixture was stirred at ambient temperature for 60 hours. The reaction mizture was then concentrated *in vacuo*, diluted with dichloromethane (100 ml), washed with water (three times, 30 ml each) and brine (40 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Following a flash silica gel chromatography (5-20% ethyl acetate/dichloromethane), 2,3-dichlorobenzoic acid-N-(5-trifluoromethyl-pyridin-2-yl)hydrazide (0.6 g, 40%) was obtained as a solid. The compound was identified by NMR spectral analysis.

Next, phosphorous oxychloride (3.2 ml, 34.3 mmol) was added to a solution of 2,3-dichlorobenzoic acid-N-(5-trifluoromethylpyridin-2-yl)hydrazide (0.6 g, 1.71 mmol) in anhydrous toluene (40 ml). The resulting mixture was stirred at reflux for 21 hours. The mixture was then poured into cold aqueous sodium hydroxide (2M, 100 ml), extracted with ethyl acetate, washed with water (40 ml) and brine (40 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Following a flash silica gel chromatography (5-50% ethyl acetate/dichloromethane), a yellow solid was obtained. The yellow solid was again chromatographed on silica gel (5-33% ethyl acetate/hexanes), and 3-(2,3-dichlorophenyl)-6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine **129** (245 mg, 45%) was obtained as an off-white solid: mp 100-101°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (s, 1H), 8.08 (d, 1H), 7.95 (d, 1H), 7.79 (d, 1H), 7.72 (d, 1H), 7.67 (m, 1H); ESI MS m/z 332 $[C_{13}H_6Cl_2F_3N_3 + H]^+$.

6.22 Example 22: Synthesis of 3-(2,6-dichlorophenyl)-6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine (131)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 1.325 g, 6.91 mmol), 4-methylmorpholine (0.76 ml, 6.91 mmol), 1-hydroxybenzotriazole hydrate (HOBt, 0.177 g, 1.31 mmol) and 5-trifluoromethylpyridyl hydrazine (68%, 1.0 g, 3.84 mmol) were added to 2,6-dichlorobenzoic acid (1.0 g, 5.76 mmol) in anhydrous 1:1 dichloromethane/acetonitrile (40 ml) at 0°C. The ice bath was removed and the

mixture was stirred at ambient temperature for 60 hours. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (100 ml), washed with water (three times, 30 ml each) and brine (40 ml), dried with magnesium sulfate, and concentrated *in vacuo*. Following a flash silica gel chromatography (5-50% ethyl acetate/dichloromethane), 2,6-dichlorobenzoic acid-N-(5-trifluoromethylpyridin-2-yl)hydrazide (0.732 g, 36%) was obtained as a solid. The compound was identified by NMR spectral analysis.

Next, phosphorous oxychloride (3.9 ml, 41.8 mmol) was added to a solution of 2,6-dichlorobenzoic acid-N-(5-trifluoromethyl-pyridin-2-yl)hydrazide (0.732 g, 2.09 mmol) in anhydrous toluene (40 ml). The mixture was stirred at reflux for 18 hours. The mixture was then poured into cold aqueous sodium hydroxide (2M, 100ml), extracted with ethyl acetate, washed with water (40 ml) and brine (40 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Following a flash silica gel chromatography (5-25% ethyl acetate/hexanes), 3-(2,6-dichlorophenyl)-6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine **131** (0.1 g, 14%) was obtained as an off-white solid: mp 104-105°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 8.10 (d, 1H), 7.78 (d, 1H), 7.72 (s, 3H); ESI MS m/z 332 $[C_{13}H_6Cl_2F_3N_3 + H]^+$.

6.23 Example 23: Inhibition of the Edg-4 Receptor by Compound 101

Figure 1 demonstrates that compound **101** specifically inhibited the Edg 4 receptor. Compound **101** did not inhibit LPA-stimulated calcium increases in HTC cells expressing Edg 2 or Edg 7 receptors and also did not inhibit S1P-stimulated calcium increases in HTC cells expressing Edg 1, Edg 3, Edg 5, or Edg 8 receptors. When tested with the Edg 4 receptor, compound **101** almost completely blocked the LPA response in concentrations between about 1 μM and about 10 μM. Figure 2 shows that compound **103** has a 2-3 fold greater potency than compound **101**, while compound **105** is less potent than compound **101**.

Figure 3 illustrates a dose response to LPA using varying concentrations of **101** (0-10 μM) in HTC cells expressing human Edg 4 receptors. The data suggests that inhibition by compound **101** may be irreversible, as demonstrated by the inability of LPA to overcome inhibition by compound **101** at concentrations as high as 10 μM.

Figure 4 demonstrates that compound **101** retained its activity when tested on endogenous Edg 4 receptors from human ovarian cancer cells (OV202). LPA-stimulated calcium responses in these cells was almost completely inhibited by 10 μM

of compound **101**. The calcium mobilization assays were conducted as described in Section 6.25 (Example 25).

Compound **101** also inhibited LPA-stimulated calcium response in another human ovarian cancer cell line, CaOV3, in a non-competitive mode (Figure 5). In this instance, the LPA response was not completely inhibited, because these cells express other LPA receptors (Edg 2 and Edg 7).

Vascular Endothelial Growth Factor, ("VEGF"), is a potent mitogenic and highly angiogenic factor that causes vascular permeability, which leads to ascites formation. Furthermore, VEGF is tumor-specific. Plasma VEGF levels are significantly elevated in patients with various tumors, including prostate and ovarian cancer (George *et al.*, **2001**, *Clin Cancer Res* 7:1932-1936; Hu *et al.*, **2001**, *Natl. Cancer Inst.* 93 (10):762-767). Therefore, the ability of Edg-receptor antagonists to block VEGF secretion from tumor cells is a particularly relevant secondary assay for potential anti-tumor therapies. Figure 6 shows that compound **101** completely blocked LPA-stimulated VEGF production in CaOV3 human ovarian cancer cells. The VEGF assays were conducted as described in Section 6.26 (Example 26).

Ovarian cancer cells are known to increase IL-8 secretion (Schwartz *et al.*, **2001**, *Gynecol. Oncol.* 81 (2):291-300). Further, expression of IL-8 has been correlated with cell metastatic potential (Singh *et al.*, **1994,** *Cancer Res.* 54(12):3242-3247). In addition to blocking production of VEGF, compound **101** also completely blocked the production of IL-8 in CaOV3 human ovarian cancer cells (Figure 7). The IL-8 assays were conducted as described in Section 6.26 (Example 26).

Since LPA is a potent mitogen, it was important to establish whether blocking Edg 4 in human ovarian cancer cells would also block proliferation. Compound **101** (10 μM) effectively abolished LPA-stimulated proliferation of CaOV3, human ovarian cancer cells over a period of 24 hours (Figure 8). The proliferation assays were conducted as described in Section 6.28 (Example 28).

LPA-stimulated chemotaxis is another important marker for angiogenesis and metastasis. Figure 9 demonstrates that LPA stimulated chemotaxis in CaOV3 human ovarian cancer cells was effectively blocked by Edg 4 antagonist **103**.

6.24 Example 24: Selective Inhibition of the Edg-4 Receptor by Compounds 101 and 103

Selectivity of illustrative compounds **101** and **103** for Edg 4 was demonstrated

in several ways. Compound **101** did not demonstrate any inhibitory activity at any of the other Edg receptors tested (Figure 1). In addition, compound **101** did not demonstrate any significant activity at various targets tested, including other Edg receptors, GPCRs, ion channels, and enzymes (Table 1). Compound **103** did not inhibit S1P induced chemotaxis in HUVEC cells, although it did inhibit LPA-stimulated chemotaxis in CaOV3 cells (Figure 10), which is mediated by the Edg-4 receptor. Table 1 demonstrates the selectivity of compounds **101** and **103** for Edg-4 relative to other Edg receptors. In addition, radioligand binding assays were conducted as described in Section 6.30 (Example 30).

Table 1: Selectivity of 101 and 103 for Edg-4

	101	**103**
Edg-1	>20	>20
Edg-2	>20	>20
Edg-3	>20	>20
Edg-4	0.67	0.32
Edg-5	>20	>20
Edg-6	>20	>20
Edg-7	>20	>20
Edg-8	>20	>20
Fold-selectivity	**>29.9**	**>62.5**

(Measurements of IC_{50}, unit = μM)

Table 1 illustrates the selectivity of illustrative compounds of the invention for Edg-4 relative to other Edg receptors. Similarly, selectivity exhibited by other compounds of the invention for Edg-4 receptors is summarized in Table 2. As shown in Table 2, the compounds of this invention show much higher efficacy for Edg-4 receptors than other Edg receptors.

Table 2: Selectivity of Various Compounds for Edg-4 Receptors

	121 (IC_{50}, μM)	**125** (EC_{50},μM)	**129** (EC_{50},μM)	**131** (EC_{50},μM)
Edg 1	>20	>25	>25	>25
Edg 2	>20	>25	>25	>25
Edg 3	>20	>25	>25	>25

Edg 4	**3.6**	**5.2**	**5.4**	**9.9**
Edg 5	>20	>25	>25	>25
Edg 6	>20	>25	>25	>25
Edg 7	>20	**2.5**	>25	>25
Edg 8	>20	>25	>25	>25
Null	-	>25	>25	>25
Fold Selectivity	**>5.6**	**>4.8**	**>4.6**	**>2.5**

6.25 Example 25: Synthesis of Compound 701

2-chlorobenzenesulfonyl isocyanate (0.13 mL, 0.89 mmol) was added to a solution of ethyl 2-amino-4, 5, 6, 7-tetrahydrobenzo[B]thiophene-3-carboxylate (0.20 g, 0.89 mmol) in benzene (2 mL) at room temperature. After 2.5 hours, the reaction mixture was filtered to provide 310 mg (79%) of **701** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.68 (s, 1H), 8.33 (m, 1H), 7.92 (br s, 1H), 7.57 (m, 2H), 7.43 (m, 1H), 4.39 (m, 2H), 2.73 (m, 2H), 2.58 (m, 2H), 1.75 (m, 4H), 1.38 (m, 3H). CI-MS: m/z = 443 [$C_{18}H_{19}ClN_2O_5S_2$ + H]. Melting Range: 222-225 °C.

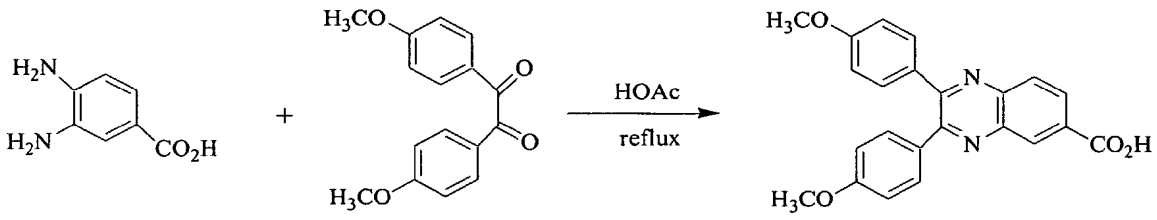
6.26 Example 26: Synthesis of 3-(2-Imino-4-oxothiazolidin-5-ylidene)-1-(toluene-4-solfonyl)-1,3-dihydro-indol-2-one (703)

A mixture of pseudothiohydantoin (789 mg, 6.80 mmol), isatin (1.00 g, 1 equiv.) and sodium acetate (1.67 g, 3 equiv.) in glacial acetic acid (20 mL) was stirred at reflux overnight. The mixture was then cooled to room temperature and the precipitates were collected by suction filtration and washed with water. The solids were further triturated with hot methanol. 3-(2-Imino-4-oxo-thiazolidin-5-ylidene)-1,3-dihydroindol-2-one was obtained as a red solid (1.47 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 9.56 (s, 1H), 9.30 (s, 1H), 8.97 (m, 1H), 7.34 (m, 1H), 7.05 (m, IH), 6.93 (m, 1H). APCI-MS: m/z 246 [$C_{11}H_7N_3O_2S$ + H]$^+$ M.P. 345 °C (decomposed).

3-(2-Imino-4-oxothiazolidin-5-ylidene)-1,3-dihydro-indol-2-one (113 mg, 0.461 mmol) in dry DMF (5 mL) was cooled in an ice bath. NaH (60% in mineral oil, 28 mg, 0.691 mmol, 1.5 equiv.) was added in one portion. The cold bath was removed and the stirring continued overnight. *p*-toluenesulfonyl chloride (97 mg,

0.51 nmuol, 1.1 equiv.) was then added and the reaction mixture was stirred for another 12 hours. DMF solvent was removed by co-evaporation with toluene. The residue was taken up with ethyl acetate (30 mL) and suction filtered. The filter cake was found to be mostly unreacted starting materials along with *p*-toluenesulfonic acid. The liquid filtrate was concentrated and subject to flash column chromatography over silica gel using methanol/dichloromethane (1:10). **703** was obtained as a red solid (15 mg, 8% yield). ^{1}H NMR (300 MHz, acetone-do) δ 8.90 (m, 1H), 7.86 (m, 2H), 7.42-7.48 (m, 3H), 7.10-7.15 (m, 1H), 7.057.08 (m, 1H), 2.45 (s, 3H). APCI-MS: m/z 400 [C,8H,3N304S2 + H]$^+$.

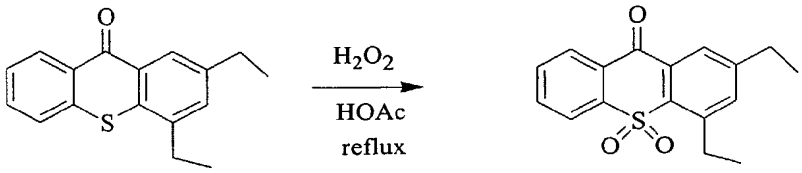
6.27. Example 27: Synthesis of Compound 729: 2,3-bis-(4-Methoxyphenyl) quinoxaline-6-carboxylic acid



A mixture of 3,4-diaminobenzoic acid (0.153 g, 1.00 mmol), 4,4'-dimethoxybenzil (0.271 g, 1.00 mmol) and acetic acid (6 mL) was stirred at reflux for 12 h, cooled to room temperature and poured into water (75 mL). The resultant solid was taken up in aqueous sodium hydroxide (2M) and washed with dichloromethane; the aqueous layer was acidified and the resultant solid was recrystallized from methanol to afford 2,3-bis-(4-methoxyphenyl)quinoxaline-6-carboxylic acid (0.171 g, 44% yield) as a yellow solid: mp 284-285 °C; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.79 (s, 1H), 8.39 (d, 1H), 8.21 (d, 1H), 7.61 (d, 4H), 6.97 (d, 4H), 3.89 (s, 7H); ESI MS m/z 387 [$C_{23}H_{18}N_2O_4$ + H]$^+$.

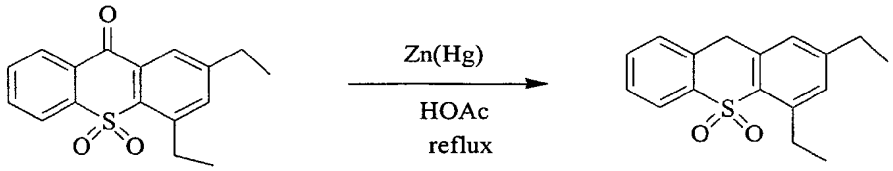
6.28. Example 28: Synthesis of Compound 731

(a) 2,4-Diethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one



Hydrogen peroxide (3.0 mL, 29.0 mmol) was added 1 mL at a time to a refluxing solution of 2,4-diethyl-thioxanthen-9-one (0.504 g, 1.88 mmol) in acetic acid (~10 mL) and allowed to stir for 2 h. The reaction was cooled to room temperature and allowed to stand 18 h. The reaction was filtered and the resulting yellow, highly viscous liquid was washed with dichloromethane and methanol, then reduced *in vacuo*. 2,4-Diethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one (0.381 g, 67% yield) was obtained as a yellow solid after recrystallization from ethanol and was identified on the basis of NMR spectral analysis.

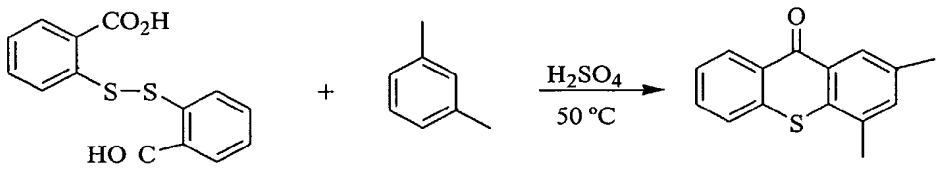
(b) 2,4-Diethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one



Zinc amalgam was formed via the addition of zinc (0.956 g, 14.6 mmol) to mercury(II) chloride (0.125 g, 0.46 mmol). To this mixture water (10 mL) was added slowly. Hydrochloric acid (0.25–0.50 mL) was added and the mixture stirred for five minutes. The mixture was decanted and the zinc amalgam was covered with acetic acid (10 mL) and hydrochloric acid (2 mL), resulting in an exotherm. 2,4-Diethyl-10,0-dioxo-10*H*-10λ^6-thioxanthen-9-one (0.350 g, 1.17 mmol) was added; the mixture was stirred at reflux for 2 h and cooled to room temperature. The mixture was decanted into water (50 mL), which resulted in a pink viscous liquid and a white precipitate; the suspension was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Flash column chromatography (silica gel, 9:1, hexanes/ethyl acetate) afforded 2,4-diethyl-9*H*-thioxanthene 10,10-dioxide (0.190 g, 57%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H), 7.45 (m, 3H), 7.08 (d, 2H), 4.23 (s, 2H), 3.25 (q, 2H), 2.65 (q, 2H), 1.37 (t, 3H), 1.24 (t, 3H); APCI MS m/z 287 $[C_{17}H_{18}O_2S + H]^+$.

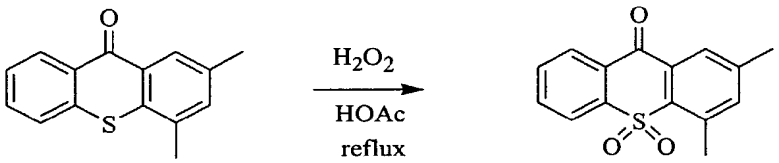
6.29 Example 29. Synthesis of Compound 733

(a) 2,4-Dimethylthioxanthen-9-one



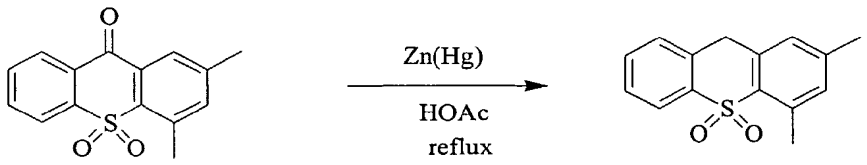
1,3-Dimethylbenzene (2.0 mL, 16.3 mmol) was added to a suspension of 2-mercapto- benzoic acid disulfide (0.950 g, 3.10 mmol) in concentrated sulfuric acid (10 mL); the resultant mixture was stirred at 50–55 °C for 1 h. The mixture was cooled and water (150 mL) was added. The resultant solid was filtered and slurried in aqueous sodium hydroxide (0.5 M), filtered and washed with water to afford 2,4-dimethylthioxanthen-9-one (0.565 g, 76% yield), which was identified by NMR spectral analysis.

(b) 2,4-Dimethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one



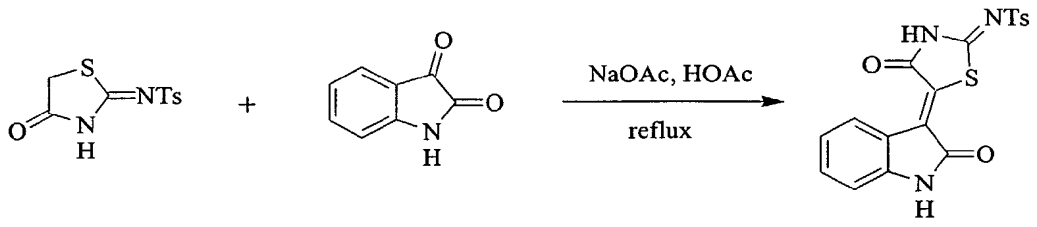
Hydrogen peroxide (30% wt., 3.0 mL, 29.0 mmol) was added dropwise to a solution of 2,4-dimethylthioxanthen-9-one (0.535 g, 2.23 mmol) in acetic acid (~10 mL) at reflux; the resultant mixture was stirred 2 h at reflux. The reaction was cooled to ambient temperature, added to water (200 mL) and allowed to stand 48 h. Filtration afforded 2,4-dimethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one (0.450 g, 74%) as a yellow solid, which was identified by NMR spectral analysis.

(c) 2,4-Dimethyl-9*H*-thioxanthene 10,10-dioxide



Water (10 mL) was added slowly to zinc amalgam, formed from the addition of zinc (1.53 g, 23.4 mmol) to mercury(II) chloride (0.167 g, 0.64 mmol). Hydrochloric acid (0.25–0.50 mL) was added and the mixture stirred for five min. The mixture was decanted and the zinc amalgam covered with acetic acid (10 mL) and hydrochloric acid (2 mL), resulting in an exotherm. 2,4-Dimethyl-10,10-dioxo-10*H*-10λ^6-thioxanthen-9-one (0.440 g, 1.62 mmol) was added and the reaction stirred at reflux for 2 h. After cooling to room temperature, the mixture was decanted into water (50 mL), which resulted in a pink viscous liquid and a white precipitate being formed; the suspension was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with aqueous sodium hydroxide (1M), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The resultant solid was recrystallized twice from ethanol to afford 2,4-dimethyl-9*H*-thioxanthene-10,10-dioxide (0.205 g, 49% yield) as a pink crystalline solid: mp 103-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H), 7.46 (m, 3H), 7.04 (d, 2H), 4.20 (s, 2H), 2.78 (s, 3H), 2.35 (s, 3H); APCI MS m/z 259 $[C_{15}H_{14}O_2S + H]^+$.

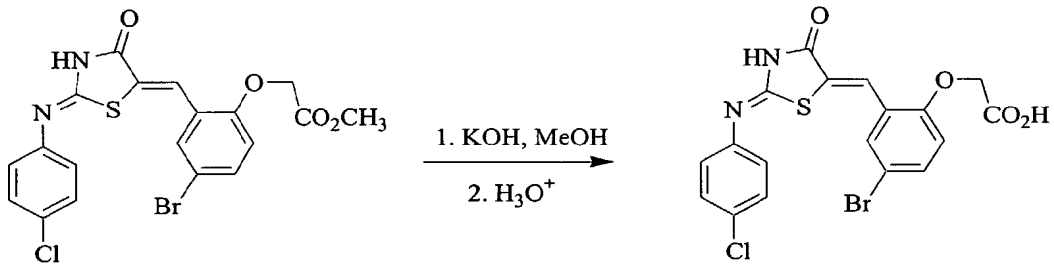
6.30. Example 30: Compound 705: 4-Methyl-*N*-[4-oxo-5-(2-oxo-1,2-dihydroindol-3-ylidene)thiazolidin-2-ylidene]-benzenesulfonamide



A mixture of 2H-indole-2,3-dione (97.0 mg, 0.655 mmol), 4-methyl-*N*-(4-oxo-thiazolidin-2-ylidene)benzenesulfonamide (177 mg, 0.665 mmol), sodium acetate (161 mg, 1.97 mmol) and acetic acid (5 mL) was heated to reflux, stirred for 15 h and cooled to ambient temperature. The resultant suspension was filtered and washed with water; the filtrate was triturated with hot methanol to afford 4-methyl-*N*-[4-oxo-5-(2-

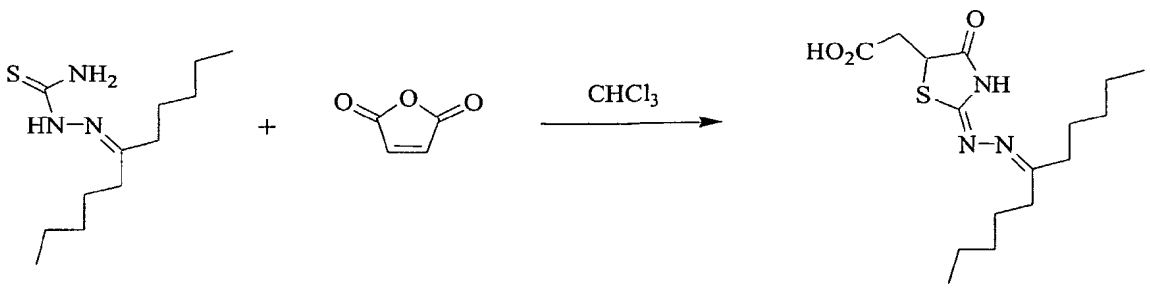
oxo-1,2-dihydroindol-3-ylidene)thiazolidin-2-ylidene]benzenesulfonamide (0.167 g, 64%) as a red solid: mp 320 °C dec; ^{1}H NMR (500 MHz, Acetone-d_6) δ 10.69 (bs, 1H), 10.23 (bs, 1H), 8.97 (d, 1H), 7.91 (d, 2H), 7.50 (d, 3H), 7.19 (t, 1H), 7.09 (d, 1H), 2.49 (s, 3H); ESI MS m/z 400 $[C_{18}H_{13}N_3O_4S_2 + H]^+$.

6.31. Example 31: Compound 707: 4-Bromo-2-[2-(4-chlorophenylimino)-4-oxothiazolidin-5-ylidenemethyl]phenoxyacetic acid



Methyl 4-bromo-2-[2-(4-chlorophenylimino)-4-oxothiazolidin-5-ylidenemethyl]phenoxyacetate (0.147 g, 0.305 mmol) was added to a solution of potassium hydroxide in methanol (3%, 20 mL) at ambient temperature; the resultant mixture was stirred for 18 h. Water (20 mL) was added and the methanol was removed by reduced pressure. The residue was cooled to 0 °C and aqueous hydrochloric acid (2M) was added to pH ~3. The solid was filtered and recrystallized from 95% ethanol to afford 4-bromo-2-[2-(4-chlorophenylimino)-4-oxothiazolidin-5-ylidenemethyl]phenoxyacetic acid (0.133 g, 93% yield) as a yellow solid: mp 272 °C dec; ^{1}H NMR, for a 1:1 mixture of E- and Z-isomers, (500 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.83 (s, 1H), 7.79 (d, 2H), 7.75 (s, 1H), 7.54 (m, 2H), 7.48 (m, 4H), 7.35 (s, 1H), 7.16 (d, 2H), 6.98 (dd, 2H), 4.80 (s, 2H), 4.79 (s, 2H), 3.40 (bs, 4H); ESI MS m/z 467 $[C_{18}H_{12}BrClN_2O_4S + H]^+$.

6.32. Example 32: Synthesis of Compound 727: 4-Oxo-2-[(1-pentylhexylidene)hydrazono]thiazolidin-5-ylacetic acid



The thiosemicarbazone (1.229 g, 5.05 mmol, *Coll. Czech. Chem. Comm.* **1997, 62**, 124) was added to a solution of maleic anhydride (0.492 g, 5.02 mmol) in chloroform (45 mL); the mixture was stirred at reflux for 1.5 h. The mixture was cooled and concentrated *in vacuo*. The residue was added to saturated ammonium chloride and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were extracted with aqueous sodium hydroxide (0.5 M, 2 x 50 mL). The combined aqueous layers were treated with hydrochloric acid (1M, ~ 75 mL), to pH 5-6. The mixture was extracted with ethyl acetate (3 x 30 mL); the organic layers were combined and concentrated *in vacuo*. The resultant solid was recrystallized from acetonitrile to afford 4-oxo-2-[(1-pentylhexylidene)hydrazono]thiazolidin-5-ylacetic acid (0.477 g, 28%) as a white solid: mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, 1H), 2.85 (dd, 1H), 2.81 (dd, 1H), 2.40 (t, 2H), 2.26 (t, 2H), 1.49 (m, 6H), 1.39 (m, 6H), 0.86 (m, 6H); ESI-MS m/z 342 $[C_{16}H_{27}N_3O_3S + H]^+$.

6.33. Example 33: Selective Inhibition of the Edg-7 Receptor by Compound 701

701 and **703** are representatives of a series of compounds that demonstrate inhibition of Edg-7 stimulated LPA responses. The compounds were tested in HTC cells expressing human Edg 7 receptors, as well as in HT1080 human fibrosarcoma cell lines that naturally express Edg 7 receptors. The rat hepatoma cell line, HTC, does not express any detectable levels of any of the known Edg receptors. Therefore, HTC proved to be a useful system because Edg-7 could be tested in isolation when recombinantly introduced into these cells. The compounds are tested in this recombinant system first, and subsequently tested in cell lines expressing Edg-7 (in addition to other Edg receptors).

Figure 17 demonstrates that **701** specifically inhibit the Edg-7 receptor. **701** did not inhibit LPA-stimulated calcium increases in HTC cells expressing Edg-2 or Edg-4 receptors and also did not inhibit S1P-stimulated calcium increases in HTC

cells expressing Edg-1, Edg-3, Edg-5, or Edg-8 in concentrations as high as 10 μM.

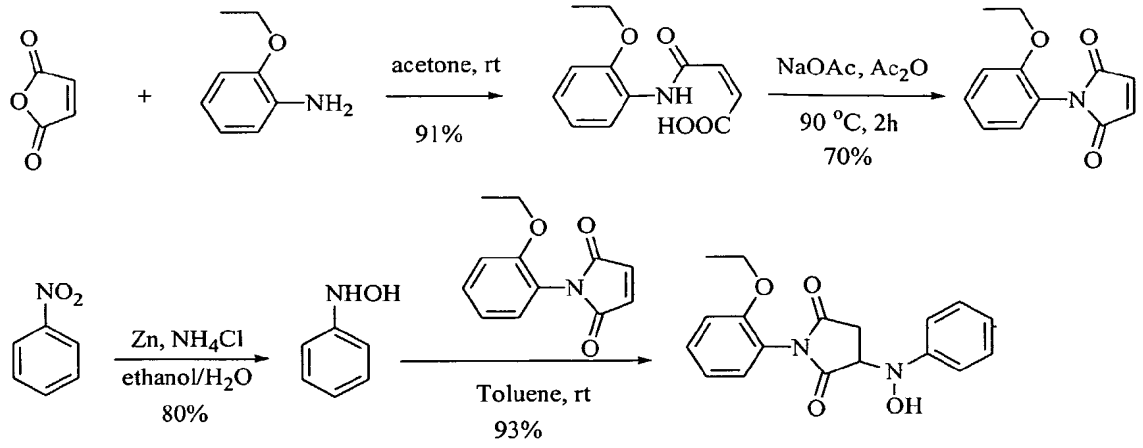
Figure 18 demonstrates that another Edg-7 antagonist, **703**, exhibited selectivity for Edg 7 when tested on HT1080 cells. The LPA-stimulated calcium mobilization was blocked by **703**, but not by the Edg 4 antagonist, 4,4,4-trifluoro-3-oxo-*N*-(5-phenyl-2H-pyrazol-3-yl)-butyramide, suggesting that in these cells, the LPA response is predominantly Edg 7 driven. The calcium mobilization assays were conducted as described in the examples below.

Selectivity of **701** for Edg-7 is also demonstrated in Tables 1 and 2. **701** did not demonstrate any significant activity at various targets tested, including other Edg receptors, GPCRs, and ion channels. Table 3 demonstrates the selectivity of **701** for Edg-7 relative to other Edg receptors and Table 4 is a list of targets, including GPCRs and ion channels, for which **701** showed no significant activity in radioligand binding assays. The radioligand binding assays were conducted as described the examples below.

6.34 Example 34: Synthesis of 1-(2-Ethoxyphenyl)-3-(hydroxyphenylamino)-pyrrolidine-2,5-dione (201)

N-(2-ethoxyphenyl)maleimide was first prepared in two steps from maleic anhydride and *o*-phenetidine in 64% overall yield (Rangnekar *et al.*, **1986**, *Ind. J. Chem.* 1986, 25B:342-344). *N*-Phenylhydroxylamine was prepared from reduction of nitrobenzene and used without purification (Bordwell *et al.*, **1996**, *J. Am. Chem. Soc.* 118:8777-8781).

N-Phenylhydroxylamine (1.90 g, *ca.* 70% purity, 12.2 mmol) was added to a solution of *N*-(2-ethoxyphenyl)maleimide (1.80 g, 8.27 mmol) in dry toluene (20 mL) and the mixture was stirred at room temperature for 12 hours. Solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes (1:4, 1:3, and 1:1)) to provide the desired compounds as an off-white solid (2.53 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 - 7.40 (m, 3H), 6.98 – 7.22 (m, 6H), 5.78 (s, 0.5H), 5.61 (s, 0.5H), 4.90 (m, 1H), 4.08 (m, 2H), 3.12 (m, 1H), 2.85 (m, 1H), 1.35 (m, 3H). APCI-MS: *m/z* 309 $[C_{18}H_{18}N_2O_4 + H - H_2O]^+$. M.p. 174-175 °C.



6.35 Example 35: Synthesis of 2-(1-Ethyl-3-methyl-5-phenyl-1H-pyrazol-4-yl)-phenol (203)

o-Hydroxyphenylacetone was prepared from *o*-tolyl acetate in a two-step process. The first step was the benzylic bromination (Loukiala *et al.*, **1997**, *Acta Chem. Scand.* 51:1162-1166), followed by intramolecular acetyl migration (Ledoussal *et al.*, **1987**, *Tetrahedron* 43:5841-5852) in 57% yield.

o-Hydroxyphenylacetone (5.89 g, 39.2 mmol), DMAP (4.79g, 39.2 mmol, 1 equivalent) and pyridine (3.2 mL, 1 equivalent) were dissolved in dry THF (200 mL). The solution was cooled with an ice bath and benzoyl chloride (5.5 mL, 1.2 equivalents) was then added slowly via syringe. The mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was diluted with ethyl acetate (400 mL) and washed with saturated aqueous NH_4Cl (100 mL x 3), dried with Na_2SO_4 and evaporated. Flash column chromatography over silica gel using ethyl acetate/hexanes (1:10, 1:8, 1:6, 1:4, and 1:3) gave benzoic acid 2-(2-oxopropyl)phenyl ester as a white crystalline solid (7.12 g, 71% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.16-8.20 (m, 2H), 7.63-7.68 (m, 1H), 7.50-7.55 (m, 2H), 7.22-7.44 (m, 4H), 3.67 (s, 2H), 2.12 (s, 3H).

Finally, benzoic acid 2-(2-oxopropyl)phenyl ester (20.33 g, 79.95 mmol), ethylhydrazine oxalate (15.01 g, 99.94 mmol, 1.25 equivalents), and acetic acid (37 mL) in ethylene glycol (70 mL) were stirred at 200-205 °C (oil bath temperature) for 90 minutes and the mixture was cooled to room temperature. (Dzvinchuk *et al.*, **1995**,

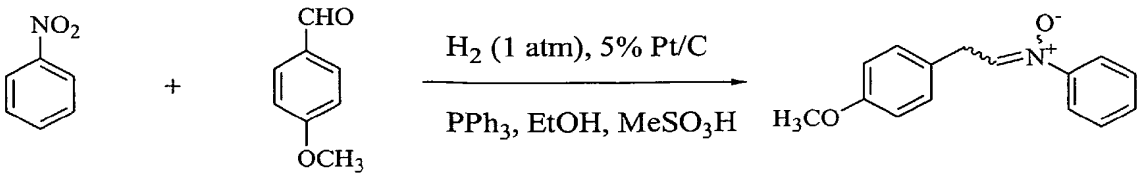
Russ. J. Org. Chem. 31:218-220). Water (500 mL) was added and the content was chilled with an ice bath. A white precipitate was collected by suction filtration and further subjected to flash chromatography on silica gel (acetone/CH_2Cl_2 (1:10, 1:8)) to provide the desired compound as a white solid (13.30 g, 60% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.35 (m, 3H), 7.18-7.21 (m, 3H), 6.98-7.01 (m, 1H), 6.83-6.86 (m, 2H), 4.99 (s, 1H), 4.12 (m, 2H), 2.21 (s, 3H), 1.44 (m, 3H). APCI-MS: *m/z* 279 $[C_{18}H_{18}N_2O + H]^+$. M.p. 164 – 165 °C. Calculated: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.41; H, 6.49; N, 10.04.

6.36. Example 36: Synthesis of Compound 211: 1-(2-Ethoxyphenyl)-3-[(4-fluorophenyl)hydroxylamino]pyrrolidine-2,5-dione

A mixture of 2'-ethoxyphenylmaleimide (0.115 g, 0.529 mmol) and 4-fluorophenylhydroxylamine (70%, 0.192 g, 1.058 mmol) in toluene (6 mL) was stirred at ambient temperature. The mixture was concentrated *in vacuo* and the residue chromatographed (silica gel, 10 to 50% ethyl acetate/hexanes) to afford 1-(2-ethoxyphenyl)-3-[(4-fluorophenyl)hydroxylamino]pyrrolidine-2,5-dione (0.153 g, 84%) as a light yellow solid: mp 123-124 C; ^1H NMR (500 MHz, $CDCl_3$) d 7.41 (m, 1H), 7.17 (m, 3H), 7.03 (m, 4H), 5.99 (s, 0.5H), 5.78 (s, 0.5H), 4.80 (m, 1H), 4.05 (m, 2H), 3.17 (m, 1H), 2.85 (m, 1H), 1.36 (t, 3H); ESI MS m/z 327 $[C_{18}H_{17}FN_2O_4 + H - H_2O]+$.

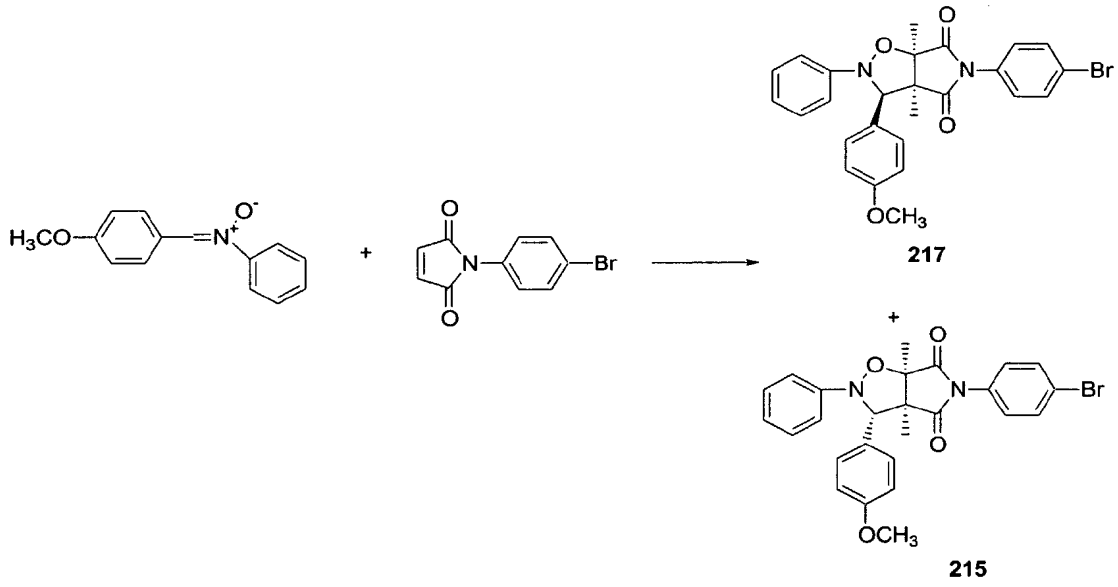
6.37. Example 37: Synthesis of Compound 215: 5-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-phenyl-*trans*-3-*cis*-3a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione and Compound 117: 5-(4-Bromophenyl)-3-(4methoxyphenyl)-2-phenyl-*cis*-3-*cis*-3a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione and Compound 113: 5-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-phenyl-3-3a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione

(a) *C*-(4-Methoxybenzyl)-*N*-phenylnitrone



Reference: *J. Org. Chem.* **1989, 54**(21), 5176-80.

A mixture of nitrobenzene (1.03 mL, 10.0 mmol), *para*-anisaldehyde (1.22 mL, 10.0 mmol), triphenylphosphine (100 mg), methanesulfonic acid (0.10 mL) and ethanol (10 mL) was purged with nitrogen gas. Platinum on carbon (100 mg, 5%, 50% water) was added and a balloon filled with hydrogen gas was connected to the reaction vessel. The resultant mixture was stirred under hydrogen atmosphere at room temperature for 18 h. The mixture was purged with nitrogen gas and filtered through Celite with cold ethanol (15 ml). Water (20 mL) was added to the filtrate at 0 °C and the resultant suspension was filtered to afford the title compound (1.08 g, 47.6% yield) as a yellow solid, which was identified on the basis of NMR and mass spectral analysis.



A mixture of *C*-(4-methoxybenzyl)-*N*-phenylnitrone (0.300 g, 1.32 mmol), *N*-(4-bromophenyl)maleimide (0.333 g, 1.32 mmol) and benzene (2.6 mL) was stirred overnight at 40 °C. The resultant suspension was cooled to room temperature and diluted with methylene chloride until a homogeneous mixture was achieved. The mixture was chromatographed (silica gel, 20% ethyl acetate/hexanes).

5-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-phenyl-*trans*-3-*cis*-3a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione eluted first and was isolated as a tan solid (0.254 g, 40.1%): mp 203-205 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 4H), 7.32 (d, 2H), 7.20 (d, 2H), 7.04 (m, 3H), 6.60 (d, 2H), 5.75 (s, 1H), 5.15 (d, 1H), 4.06 (d, 1H), 3.86 (s, 3H); APCI MS m/z 481 $[C_{24}H_{19}BrN_2O_4 + H]^+$.

5-(4-Bromophenyl)-3-(4methoxyphenyl)-2-phenyl-*cis*-3-*cis*-3a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione eluted second and was isolated as a tan solid (0.198 g, 31.3% yield): mp 206-208 °C dec;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 2H), 7.39 (d, 2H), 7.25 (d, 2H), 7.15 (d, 3H), 7.03 (d, 2H), 6.90 (d, 2H), 5.30 (d, 1H), 4.90 (d, 1H), 4.08 (t, 1H), 3.78 (s, 3H); APCI MS m/z 481 $[C_{24}H_{19}BrN_2O_4 + H]^+$.

Illustrative compound **213** is formed by mixing **215** and **217** to form a 1:1 mixture.

6.38. Example 38: Synthesis of Compounds 207 and 209: Separation of Enantiomers of Compound 201

Separation of enantiomers of 1-(2-Ethoxyphenyl)-3-(hydroxyphenylamino)-pyrrolidine-2,5-dione was achieved by a chiral separation using Chiracel OD (50 x 500 mm) column (Eluent: 100% ethanol; flow rate: 60.0 mL/min; monitoring wavelength: 260 nm). The enantiomer which eluted first under the listed conditions was defined as 'Enantiomer A', while the one which eluted later was defined as 'Enantiomer B'. Compound 107 (Enantiomer A) Alpha-D = -32deg (c=0.15, methanol). Compound 109 (Enantiomer B) Alpha-D = +5.1deg (c=0.45, methanol).

6.39 Example 39: Inhibition of the Edg-2 Receptor by Compound 201

Figure 19 demonstrates compound **201** specifically inhibit the Edg 2 receptor. Compound **201** did not inhibit LPA-stimulated calcium increases in HTC cells expressing Edg-4 or Edg-7 receptors and also did not inhibit S1P-stimulated calcium increases in HTC cells expressing Edg 1, Edg 3, Edg 5, or Edg 8 receptors.

Figure 20 demonstrates that compound **203** specifically inhibited the Edg 2 receptor. Compound **203** did not inhibit LPA-stimulated calcium increases in HTC cells expressing Edg 4 or Edg 7 receptor and also did not inhibit S1P-stimulated calcium increases in HTC cells expressing Edg 1, Edg 3, Edg 5, or Edg 8 receptors.

Figure 21 demonstrates that Edg-2 inhibitor **203** inhibited LPA-stimulated calcium mobilization in immortalized ovarian surface epithelial cells. LPA-stimulated calcium mobilization in these cells was almost completely inhibited by 10 μM **203**. However, the same concentration of Edg-4 antagonist, 4,4,4-trifluoro-3-oxo-*N*-(5-phenyl-2H-pyrazol-3-yl)-butyramide **101**, had little to no effect on calcium mobilization. The calcium mobilization assays were conducted as described in Section 6.8 (Example 8).

Figure 22 demonstrates that Edg-2 antagonist **203** reverses the inhibitory effects of LPA on forskolin-stimulated cAMP production, whereas Edg-4 antagonist **101** had little to no effect on reversing LPA inhibition of cAMP production. The cAMP assays were conducted as described in Section 6.12 (Example 12).

Fig. 23 illustrates a dose response to LPA using varying concentrations of compound **201** (0-10μM) to demonstrate the inhibition of LPA-stimulated calcium mobilization in A431 human epitheloid carcinoma cells by Edg-2 antagonist **201**. The calcium mobilization assay was conducted as described in Section 6.8 (Example 8).

Fig. 24 illustrates the inhibition of LPA-stimulated calcium mobilization in A431 human epitheloid carcinoma cells by Edg-2 antagonists **201** and **203**, but not Edg-4 antagonist, **101**. The calcium mobilization assays were conducted as described in Section 6.8 (Example 8).

6.40 Example 40: Selective Inhibition of the Edg-2 Receptor by Compounds 201 and 203

Selectivity of compounds **201** and **203** for Edg-2 was demonstrated in several ways. First, compounds **201** and **203** did not demonstrate any inhibitory activity at any of the other Edg receptors tested (Figures 19 and 20). Second, compounds **201** and **203** did not demonstrate any significant activity at various targets tested, including other GPCRs, ion channels, and enzymes (Tables 5 and 6). Table 5 demonstrates the selectivity of compounds **201** and **203** for Edg-2 relative to other Edg receptors and Table 6 is a list of targets, including GPCRs and ion channels, for which compound **201** showed no significant activity in radioligand binding assays. The radioligand binding assays were conducted as described in Section 6.13 (Example 13).

6.41 Example 41: Synthesis of 3-methyl-2-phenyl-quinoline-4carboxylic acid 4-fluoro-benzylamide (Compound 301)

3-Methyl-2-phenylquinoline-4-carboxylic acid was prepared by a Pfitzinger reaction (*J. Org. Chem.* **1950**, 15:511-516). Propiophenone (3.3 mL, 1.2 equiv.) was added to a solution of isatin (3.00 g, 20.0 mmol) in ethanol (95%, 30 mL), followed by the addition of KOH pellets (86%, 3.91g, 3 equiv.). The light brown mixture was stirred at 80 °C (oil bath temperature) for 40 hours. Solvent was removed *in vacuo* and the resulting solid residue was dissolved in water (50 mL), extracted with ether (30 mL X 2) to remove any un-reacted starting materials. The aqueous layer was then cooled with an ice bath and acidified with concentrated aqueous HCl until pH ~ 3. The white precipitate was collected by suction filtration, washed with water and dried in a vacuum oven (30 °C) overnight. The white solid was essentially pure carboxylic acid (5.10g, 97% yield) and was used for the next step without further purification. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.50-8.08 (m, 9H), 2.46 (s, 3H).

3-Methyl-2-phenylquinoline-4-carboxylic acid (1.00 g, 3.80 mmol) was then dissolved in dry THF/CH_3CN (70 mL/30 mL). 1 -Hydroxy-7-azabenzotriazole (1.31 g, 9.60 mmol, 2.5 equiv), 4-fluorobenzylamine (0.67 mL, 5.85 mmol, 1.50 equiv) were then added and the mixture was cooled in an ice bath. EDC·HCl (1.15 g, 5.99 mmol, 1.58 equiv.) was added in one portion. The ice bath was removed 15 minutes later and the reaction mixture was stirred at room temperature overnight. Organic solvents were removed *in vacuo*, the residue was taken up in dichloromethane (240 mL), washed with water (60 mL X 2) and brine (150 mL), dried with Na_2SO_4 and evaporated. Flash column chromatography over silica gel (ethyl acetate/dichloromethane (1:20, 1 :10)) gave **301** as a white crystalline solid (1.15 g, 82% yield). ^{1}H NMR (300 MHz, CDC13) δ 8.12 (m, lH), 7.77 (m, 1H), 7.69 (m, 1H), 7.39-7.58 (m, 8H), 7.08 (m, 2H), 6.20 (m, 1H), 4.76 (m, 2H), 2.41 (s, 3H). APCI-MS: m/z 371 $[C24H19FN20 + H]^+$. M.P. 190-191 °C.

6.42 Example 42: Alternate Synthesis of Compound 301

2-chlorobenzenesulfonyl isocyanate (0.13 mL, 0.89 mmol) was added to a solution of ethyl 2-amino-4, 5, 6, 7-tetrahydrobenzo[B]thiophene-3-carboxylate (0.20 g, 0.89 mmol) in benzene (2 mL) at room temperature. After 2.5 hours, the reaction mixture was filtered to provide 310 mg (79%) of **301** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.68 (s, 1H), 8.33 (m, 1H), 7.92 (br s, 1H), 7.57 (m, 2H), 7.43 (m, 1H), 4.39 (m, 2H), 2.73 (m, 2H), 2.58 (m, 2H), 1.75 (m, 4H), 1.38 (m, 3H). CI-MS: m/z = 443 [$C_{18}H_{19}ClN_2O_5S_2$ + H]. Melting Range: 222-225 °C.

6.43 Example 44: [2-(2,4,6-Trimethyl-phenylamino)-benzo[1,3]-dioxol-2-yl]-carbamic acid ethyl ester (303)

303 is commercially available and was obtained from Asinex, Moscow, Russia (Vendor number BAS 0246895

6.44 Example 43: Selective Inhibition of the Edg-3 Receptor by Compound 301

301 and **303** are representatives of a series of compounds that demonstrate inhibition of Edg-3 stimulated S1P responses. The compounds were tested in HTC cells expressing human Edg-3 receptors, as well as in NIH 3T3 cell lines that naturally express Edg-3 receptors. The rat hepatoma cell line, HTC, does not express any detectable levels of any of the known Edg receptors. Therefore, HTC proved to be a useful system because Edg 3 could be tested in isolation when recombinantly introduced into these cells. The compounds were tested in this recombinant system first, and subsequently tested in cell lines expressing Edg-3 (in addition to other Edg receptors).

Figure 25 demonstrates that **301** specifically inhibited Edg-3 receptors. **301** did not inhibit LPA-stimulated calcium increases in HTC cells expressing Edg-2, Edg-4 or Edg-7 receptors and also did not inhibit S1P-stimulated calcium increases in HTC cells expressing Edg-1, Edg-5, or Edg-8 in concentrations as high as 20 μM.

Figure 26 demonstrates that another Edg-3 antagonist, **303**, blocked S1P-stimulated calcium responses, suggesting that in these cells, the S1P response is predominantly Edg 3 driven. The calcium mobilization assay was conducted as described in Section 6.4 (Example 4).

Selectivity of **301** for Edg-3 is also demonstrated in Tables 7 and 7. **301** did not demonstrate any significant activity at various targets tested, including other Edg receptors, GPCRs, and ion channels. Table 7 demonstrates the selectivity of **301** for Edg-3 relative to other Edg receptors. Table 8 is a list of targets, including GPCRs and ion channels, against which **101** (10 μM) showed no activity in standard binding assays. The radioligand binding assays were conducted as described in Section 6.9 (Example 9).

6.45 Example 45: Intracellular Calcium Measurement Assays

LPA receptors such as Edg-2, Edg-4 and Edg-7, couple to calcium effector pathways, and result in increases in intracellular calcium following receptor activation (An *et al.*, *Molecular Pharmacology*, 54:881-888, 1998, incorporated herein by reference). This biological response lends itself to a very efficient, high-throughput screen using a Fluorescence Imaging Plate Reader (FLIPR; Molecular Devices, Sunnyvale, CA). The FLIPR system is a real-time, cell-based assay system with continuous fluorescence detection using a cooled CCD camera. The FLIPR system was used to developing an Edg receptor screen.

Rat hepatoma cells stably expressing Edg-4 receptor were plated on 384-well plates and loaded with a calcium dye loading kit (Molecular Devices, Sunnyvale, CA) for 1 hour at room temperature. Cells were then placed on the FLIPR^{354} (Molecular Devices, Sunnyvale, CA) and excited by an argon laser at 488 nm. The data for the entire 384-well plate was updated every second. An integrated robotic pipettor allowed for simultaneous compound addition into each individual well in the plate.

Figures 11 through 13 demonstrate the LPA induced calcium mobilization by the compounds **101**, **103**, **107** and **113**. When the rat hepatoma cells were transfected by human Edg-4, all of the compounds completely inhibited LPA-stimulated calcium responses at 5-10 μM (Figure 11). However, the inhibition varied when the rat hepatoma cells were transfected with pooled rat Edg-4 clones (Figure 12) or pooled mouse Edg-4 clones (Figure 13). Similar tests for compound **125** in HTC cells and CaOV-3 cells are shown in Figures 15 and 16, respectively.

The FLIPR system was also used to developing an Edg-7 receptor screen. Rat hepatoma cells stably expressing Edg-7 receptor were plated on 384-well plates and loaded with a calcium dye loading kit (Molecular Devices, Sunnyvale, CA) for 1 hour at room temperature. Cells were then placed on the FLIPR^{384} (Molecular Devices, Sunnyvale, CA) and excited by an argon laser at 488 nm. The data for the entire 384-well plate was updated every second. An integrated robotic pipettor allowed for simultaneous compound addition into each individual well in the plate.

The FLIPR system was again used to developing an Edg-2 receptor screen. Rat hepatoma cells stably expressing Edg-2 receptor were plated on 384-well plates and loaded with a calcium dye loading kit (Molecular Devices, Sunnyvale, CA) for 1 hour at room temperature. Cells were then placed on the FLIPR^{384} (Molecular

Devices, Sunnyvale, CA) and excited by an argon laser at 488 nm. The data for the entire 384-well plate was updated every second. An integrated robotic pipettor allowed for simultaneous compound addition into each individual well in the plate.

6.46 Example 46: Intracellular Calcium Measurement Assays

S1P receptors such as Edg-3, also couple to calcium effector pathways, and result in increases in intracellular calcium following receptor activation (An, 1998, J. Cell Biochem. Supp 30-31:147-157). This biological response lends itself to a very efficient, high-throughput screen using a Fluorescence Imaging Plate Reader (FLIPR; Molecular Devices, Sunnyvale, CA). The FLIPR system is a real-time, cell-based assay system with continuous fluorescence detection using a cooled CCD camera. The FLIPR system was used to developing an Edg-3 receptor screen. Rat hepatoma cells stably expressing Edg-3 receptor were plated on 384-well plates and loaded with a calcium dye loading kit (Molecular Devices, Sunnyvale, CA) for 1 hour at room temperature. Cells were then placed on the FLIPR^{384} (Molecular Devices, Sunnyvale, CA) and excited by an argon laser at 488 nm. The data for the entire 384-well plate was updated every second. An integrated robotic pipettor allowed for simultaneous compound addition into each individual well in the plate.

6.47 Example 47: IL-8 and VEGF Assays

IL-8 and VEGF assays were performed by standard enzyme-linked immunosorbent assay ("ELISA") techniques. Cells were cultured in a 96 well format, serum starved overnight, and treated with LPA or S1P (doses range from 0.1-10 μM in serum free medium) for 24 hours. Cell supematants were then collected to measure the amount of IL-8 secreted.

The assay was a standard sandwich ELISA in which an anti-IL-8 or VEGF capture antibody was adsorbed to a plastic dish. Cell supematants containing IL-8 or VEGF were added to the dish, and then an anti-IL-8/VEGF biotinylated detection antibody and streptavidin-HRP were added.

Detection was via the addition of a substrate solution and colorimetric reading using a microtiter plate reader. The level of IL-8 or VEGF was interpolated by non-linear regression analysis from a standard curve.

All reagents were from R&D Systems, Minneapolis, MN: MAB208 and AF-293-NA (capture antibody for IL-8 and VEGF respectively), BAF2O8 and BAF-293

(detection Ab for IL-8 and VEGF respectively), 208-IIL-010 and 293-VE-010 (recombinant human IL-8 protein standard and recombinant human VEGF protein standard respectively), DY998 (streptavidin-HRP), DY999 (substrate solution).

6.48 Example 48: Migration and Invasion Assays

Cells were plated in a 24 well format using Fluoroblok filter insert plates (8 μM pore size) or Fluoroblok matrigel coated filter insert plates (Becton Dickinson, San Diego, CA). The assay was a modified Boyden Chamber assay in which a cell suspension (1 x 10^5 cells/ml) was prepared in serum free medium and added to the top chamber. LPA or S1P (doses ranged from 0.1-10 μM in serum free medium) was added to the bottom chamber. Following a 20-24 hour incubation period, the number of cells migrating or invading into the lower chamber was quantitated by transferring the filter insert into a fresh 24-well plate containing 4 μg/ml calcein AM (Molecular Probes, Sunnyvale, CA) in Hank's Balanced Salt Solution and staining for one hour.

Detection was via fluorescent readout at 450 nm excitation/530 nm emission using a fluorimeter. The level of fluorescence correlated with cell number.

For most cells types, no further manipulation was required. For CaOV3 human ovarian cancer cells, however, it was necessary that the cells be serum starved overnight prior to preparing the cell suspension. In addition, the filter inserts were coated with a solution of 1 mg/ml rat-tail Collagen I (BD, SanDiego, CA).

6.29 Example 49: Proliferation Assay

Cells were plated in a 96 well format. Treatments were performed directly without any serum starvation, and typically included LPA or S1P doses in a range from 0.1-10 μM in serum free medium. Cells were treated for 24-48 before the extent of cellular proliferation was measured.

The assay was performed using the ViaLight HS kit from BioWhittaker, Rockland, ME, which is based upon the bioluminescent measurement of ATP that is present in all metabolically active cells. The reaction utilized an enzyme, luciferase, which catalyzes the formation of light from ATP and luciferin. The emitted light intensity was linearly related to the ATP concentration, which correlated with cell number.

Measurement of cell proliferation required the extraction of ATP by the addition of Nucleotide Releasing Reagent, followed by the addition of the ATP

Monitoring Reagent (both provided in kit). Detection was via chemiluminescence using the EG&G Berthold Luminometer, Gaithersburg, MD.

6.50 Example 50: cAMP Assay

Cells were plated in a *96* well format. Treatments were performed directly without any serum starvation. The cells were treated with forskolin to induce cAMP production, followed by LPA or S1P doses in the range from 0.1-10 μM in serum free medium. Following a 30-minute incubation period, the cells were lysed and the level of cAMP was determined.

The cAMP assay was performed using the Tropix cAMP-Screen (Applied BioSystems, Foster City, CA). The screen is a competitive immunoassay that utilizes a 96 well assay plate precoated with an anti-cAMP antibody. Cell lysates were added to the precoated plate, along with a cAMP-AP conjugate and a secondary anti-cAMP antibody.

Detection was performed using a substrate solution and chemiluminescent readout. The level of chemiluminescence was inversely proportional to the level of cAMP and was calculated from a standard curve.

6.51 Example 51: Pharmacology Profiling (Selectivity Assays)

In order to test the selectivity of compounds, various enzyme assays as well as radioligand binding assays were performed using numerous non-Edg receptor targets as listed below.

Enzyme Assays:

1. Phosphodiesterase PDE1: (Nicholson *et al.*, 1991, *Trends Pharmacol. Sci.* 12:19-27).

Source: Bovine heart

Substrate: 1.01 μM [^{3}H]cAMP+cAMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None;

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, 2 mM CaCl2, 10 unit Calmodulin, pH 7.5

Quantitation Method: Quantitation of [^{3}H]adenosine

Significance Criteria: ≥ 50% of max stimulation or inhibition

2. **Phosphodiesterase PDE2**: (Nicholson *et al.*, **1991,** *Trends Pharmnacol. Sci.* 12:19-27).

Source: Human platelets

Substrate: 25.1 μM [^{3}H]cAMP + cAMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, pH 7.5

Quantitation Method: Quantitation of [^{3}H]adenosine

Significance Criteria: ≥ 50% of max stimulation or inhibition

3. Phosphodiesterase PDE3: (Nicholson *et al.*, **1991,** *Trends Pharmacol. Sci.* 12:19-27).

Source: Human platelets

Substrate: 1.01 μM [^{3}H]cAMP + cAMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, pH 7.5

Quantitation Method: Quantitation of [^{3}H]adenosine

Significance Criteria: ≥ 50% of max stimulation or inhibition

4. Phosphodiesterase PDE4: (Cortijo *et al.*, **1993**)

Source: Human U937 cells

Substrate: 1.01 μM {[^{3}H]cAMP + cAMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, pH 7.5

Quantitation Method: Quantitation of [^{3}H]adenosine

Significance Criteria: a 50% of max stimulation or inhibition

5. Phosphodiesterase PDE5: (Nicholson *et al.*, **1991**, *Trends Pharmacol. Sci.* 12:19-27).

Source: Human platelets

Substrate: 100 μM [^{3}H]cGMP + cGMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, pH 7.5

Quantitation Method: Quantitation of [^{3}H]guanosine

Significance Criteria: a 50% of max stimulation or inhibition

6. Phosphodiesterase PDE6: (Gillespie and Beavo, **1989**)

Source: Bovine retinal rod outer segments

Substrate: 100 μM [^{3}H]cGMP + cGMP

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: None

Incubation Time/Temp: 20 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 5 mM MgCl2, pH 7.5

Quantitation Method: Quantitation of [^{3}H]gnanosine

Significance Criteria: $\geq$ 50% of max stimulation or inhibition

7. Phospholipase PLA_2-I (Katsumata *et al.*,**1986**, *Anal. Biochem.*, 154:676-681).

Source: Porcine pancreas

Substrate: 0.03 μCi 1-Palmitoyl-2-{1 -^{14}C]oleoyl-3- phosphatidylcholine

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: 5 minutes at 37 °C

Incubation Time/Temp: 5 minutes at 37 °C

Incubation Buffer: 0.1 M glycine-NaOH, 20 M EDTA, pH 9.0

Quantitation Method: Quantitation of [^{14}C]oleate

Significance Criteria: $\geq$ 50% of max stimulation or inhibition

8. Phospholipase PLA_2-II (Katsumata *et al.*, **1986**, *Anal. Biochem.* 154:676-681).

Source: Crotalus atrox

Substrate: 0.03 μCi 1-Palmitoyl-2-[1-^{14}C]oleoyl-3-phosphatidylcholine

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: 5 minutes at 37°C

Incubation Time/Temp: 5 minutes at 37°C

Incubation Buffer: 0.1 M glycine-NaOH, 20 M EDTA, pH 9.0

Quantitation Method: Quantitation of [^{14}C]oleate

Significance Criteria: ≥50% of max stimulation or inhibition

9. **Phospholipase PLC** (Hergenrother *et al,* **1995**, *Anal. Biochem.* 229:313-316).

Source: Bacillus cereus

Substrate: 400 μM 1,2-Dihexanoyl sn-glycerol-3-phosphocholine

Vehicle: 1 % DMSO

Pre-Incubation Time/Temp: 10 minutes at 37°C

Incubation Time/Temp: 5 minutes at 37 °C

Incubation Buffer: 0.1 M 3,3-dimethylglutaric acid, pH 7.3

Quantitation Method: Spectrophotometric quantitation of phosphorylcholine

Radioligand Binding Assays:

1. Adenosine A_1 (Liebert *et al.,* **1992,** *Biochem. Biophys. Res. Commun.* 187:919-926).

Source: Human recombinant CHO cells

Ligand: 1 nM ^{3}H DPCPX

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 90 minutes at 25 °C

Incubation Buffer: 20 mM HEPES pH 7.4, 10 mM $MgCl_2$, 100 mM NaCl

NonSpecific Ligand: 100 μM R(-)-PIA

K_d: 1.4 nM*

B_{max}: 2.7 pmol/mg Protein*

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: O 50% of max stimulation or

Quantitation Method: Radioligand Binding inhibition

Significance Criteria: ≥ 50% of max stimulation or inhibition

2. Adenosine A_{2A} (Varani *et al.*, **1996,** *Br. J. Pharmacol.* 117:1693-1701)

Source: Human recombinant HEK-293 cells

Ligand: 0.05 μM ^{3}H CGS-21680

Vehicle: 0.4 % DM50

Incubation Time/Temp: 90 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4. 10 mM $MgCl_2$, 1 mM EDTA, 2 U/mL adenosine deaminase

NonSpecific Ligand: 50 μM NECA

K_d: 0.064 μM *

B_{max}: 7 pmol/mg Protein*

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

3. Adrenergic α_{1A} (Michel *et al.*, **1989,** *Br. J. Pharmacol.* 98:883-889).

Source: Wistar Rat submaxillary gland

Ligand: 0.25 nM ^{3}H Prazosin

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 0.5 mM EDTA, pH 7.4

NonSpecific Ligand: 10 μM Phentolamine

K_d: 0.17 nM*

B_{max}: 0.18 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

4. Adrenergic α_{1A} (Uhlcn *et al.*, **1994,** *J. Pharmacol. Exp. Ther.* 271:1558)

Source: Human recombinant insect Sf9 cells

Ligand: 1 nM ^{3}H MK-912

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 75 mM Tris-HCl, pH 7.4, 12.5 mM $MgCl_2$, 2 mM EDTA

NonSpecific Ligand: 10 μM WB-4 101

K_d: 0.06 nM*

B_{max}: 4.6 pmollmg Protein*

Specific Binding: 95% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

5. Adrenergic β_1, (Feve *et al.,* **1994,** *Proc. Natl. Acad. Sci. USA* 91:5677-5681)

Source: Human recombinant Rex 16 cells

Ligand: 0.3 nM ^{125}I Cyanopindolol

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 2 hours at 25 °C

Incubation Buffer: 50mM Tris-HCl, 5 mM EDTA, 1.5 mM $CaCl_2$, 120 mM NaCl, 1.4 mM ascorbic acid, 10mg/L BSA, pH 7.4

NonSpecific Ligand: 100 μM S(-)-Propranolol

K_d: 0.041 nM *

B_{max}: 0.072 pmol/mg Protein*

Specific Binding: 95% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

6. Adrenergic β2 (McCrea and Hill, **1993**, *Brit. J Pharmacol.* 110:619-626).

Source: Human recombinant CHO-NBR1 cells

Ligand: 0.2 nM ^{3}H CCGP-12177

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 0.5 mM EDTA, 5.0 mM $MgCl_2$, 120 mM NaCl, pH 7.4

NonSpecific Ligand: 10 μM ICI-118551

K_d: 0.44nM*

B_{max}: 0.437 pmol/mg Protein*

Specific Binding: 95% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

7. Adrenergic, Norepinephrine Transporter (Galli *et al.*, **1995**, *J. Exp. Biol.* 198:2197-2212).

Source: Human recombinant MDCK cells

Ligand: 0.2 nM ^{125}I RTI-55

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 3 hours at 4°C

Incubation Buffer: 50 mM Tris-HCl, 100 mM NaCl, 1 μM leupeptin, 10 μM PMSF, pH 7.4

NonSpecific Ligand: 10 μM Desipramine

K^d: 0.024 μM *

B_{max}: 2.5 pmol/mg Protein*

Specific Binding: 75% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

8. Calcium Channel Type L, Dihydropyridine (Ehlert *et al.*, **1982,** *Life Sci.* 30:2191-2202).

Source: Wistar Rat cerebral cortex

Ligand: 0.1 nM ^{3}H Nitrendipine

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 90 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.7

NonSpecific Ligand: 1 μM Nitrendipine

K_d: 0.18nM*

B_{max} 0.23 pmol/mg Protein*

Specific Binding: 91% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

9. Cannabinoid CB_1 (Felder *et al.*, **1995,** *Mol. Pharmacol.* 48:443-450).

Source: Human recombinant HEK-293 cells

Ligand: 8 nM ^{3}H WIN-55,212-2

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 90 minutes at 37 °C

Incubation Buffer: 50 mM Hepes, pH 7.0, 5mg/mL BSA

NonSpecific Ligand: 10 μM WIN-55,212-2

K_d: 0.3 μM *

B_{max}: 2.4 pmol/mg Protein*

Specific Binding: 70% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

10. Dopamine D_1 (Dearry *et al.*, **1990,** *Nature* 347:72-76).

Source: Human recombinant CHO cells

Ligand: 1.4 nM ^{3}H SCH-23390

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 2 hours at 37 °C

Incubation Buffer: 50mM Tris-HCl, pH 7.4, 150 mM NaCl, 1.4 mM ascorbic acid, 0.001% BSA

NonSpecific Ligand: 10 μM (+)-Butaclamol

K_d: 1.4 nM*

B_{max}: 0.63 pmol/mg Protein*

Specific Binding: 95% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

11. Dopamine D_{2L} (Bunzo *et al.*, **1988,** *Nature* 336:783-787).

Source: Human recombinant CHO cells

Ligand: 0.16 nM ^{3}H Spiperone

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 2 hours at 25 °C

Incubation Buffer: 50mM Tris-HCl, pH 7.4, 150mM NaCl, 1.4mM ascorbic acid, 0.00 1% BSA

NonSpecific Ligand: 10 μM Haloperidol

K_d: 0.08 nM*

B_{max}: 0.48 pmol/mg Protein*

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

12. $GABA_A$, Agonist Site (Enna and Snyder, **1976,** *Mol Pharmacol.* 13:442-453).

Source: Wistar Rat brain (minus cerebellum)

Ligand: 1 nM ^3H Muscimol

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 10 minutes at 4°C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4

NonSpecific Ligand: 0.1 μM Muscimol

K_d: 3.8 nM*

B_{max}: 1.8 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

13. Glutamate, NMDA, Phencyclidine (Goldman *et al.,* **1985,** *FEBS Lett.* 190:333-336).

Source: Wistar Rat cerebral cortex

Ligand: 2 nM ^3H Idazoxan

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 30 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 0.5mM EDTA, pH 7.4

NonSpecific Ligand: 0.1 μM MK-801 (Dizolcipine)

K_d: 4 nM*

B_{max}: 0.78 pmol/mg Protein*

Specific Binding: 94% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

14. Histamine H_1, Central (Hill *et al.*, **1978,** *J. Neurochem.* 31:997-1004).

Source: Guinea pig cerebellum

Ligand: 1.75 nM ^{3}H Pyrilamine

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 50 mM K-Na phosphate buffer pH 7.4 at 25°C

NonSpecific Ligand: 1 μM Pyrilamine

K_d: 0.23 nM *

B_{max}: 0.198 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

15. Imidazoline I_2, Central (Brown *et al.*, **1990,** *Br. J. Pharmacol.* 99:803-809).

Source: Wistar Rat cerebral cortex

Ligand: 2 nM ^{3}H Idazoxan

Vehicle: 0.4% DMSO

Incubation Time/Temp: 30 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, 0.5mM EDTA, pH 7.4 at 25°C

NonSpecific Ligand: 1 μM Idazoxan

K_d: 4nM*

B_{max}: 0.14 pmol/mg Protein*

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

16. Muscarinic M_2 (Delmendo *et al.*, **1989,** *Br. J. Pharmacol.* 96:457-464).

Source: Human recombinant insect Sf9 cells

Ligand: 0.29 nM ^{3}H N-Methylscopolamine (NMS)

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4 10 mM $MgCl_2$, 1mM EDTA

NonSpecific Ligand: 1 μM Atropine

K_d: 0.16 nM*

B_{max}: 4.9 pmol/mg Protein*

Specific Binding: 96% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

17. Nicotinic Acetylcholine, Central (Pabreza *et al.*, **1991**, *Mol. Pharmacol.* 39:9-12).

Source: Wistar Rat brain

Ligand: 2 nM ^{3}H Cytisine

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 75 minutes at 4 °C

Incubation Buffer: 50 mM Tris-HCl, 120 mM NaCl, 5mM KCl, 1 mM$MgCl_2$, 2.5 mM $CaCl_2$, pH 7.4

NonSpecific Ligand: 100 μM Nicotine

K_d: 1 nM *

B_{max}: 0.026 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

18. Opiate μ (Wang *et al.*, **1994,** *FEBS Lett.* 338:217-222).

Source: Human recombinant CHO-K1 cells

Ligand: 0.6 nM ^{3}H Diprenorphine

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4

NonSpecific Ligand: 10 μM Naloxone

K_d: 0.41 nM *

B_{max}: 3.8 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

19. Phorbol Ester (Ashendel, **1985,** *Biochem. Biophys. Acta* 822:219-242).

Source: ICR Mouse brain

Ligand: 3 nM ^{3}H PDBu

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 25 °C

Incubation Buffer: 20 mM Tris-HCl, containing 5 mM $CaCl_2$, pH 7.5 at 25 °C

NonSpecific Ligand: 1 M PDBu

K_d: 8.7nM*

B_{max}: 26 pmol/mg Protein*

Specific Binding: 80% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

20. Platelet-Derived Growth Factor (PDGF) (Williams *et al.,* **1984,** *J. Biol. Chem.* 259:5287-5294).

Source: Mouse 3T3 cells

Ligand: 0.02 nM ^{125}I PDGF

Vehicle:0.4 % DMSO

Incubation Time/Temp: 45 minutes at 25 °C

Incubation Buffer: HBSS, 2 mg/ml BSA, 1 mM $MgCl_2$, 1 mM $CaCl_2$

NonSpecific Ligand: 0.1 nM PDGF

K_d: 0.012 nM*

B_{max}: 3100 R/cell Receptor/cell*

Specific Binding: 88% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

21. Potassium Channel [K_{ATP}] (Gaines *et al.,* **1988,** *J. Biol. Chem.* 263:2589-2592).

Source: Syrian hamster pancreatic beta cells HIT-T15

Ligand: 5 nM ^{3}H Glyburide

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 2 hours at 25 °C

Incubation Buffer: 50 mM MOPS, 0.1 mM $CaCl_2$, pH 7.4

NonSpecific Ligand: 10 μM Glyburide

K_d: 0.64nM*

B_{max}: 1 pmol/mg Protein*

Specific Binding: 90% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

22. Sigma σ_1 (Ganapathy *et al.*, **1999**, *Pharmacol. Exp. Ther.* 289:251-260).

Source:Human Jurkat cells TIB-152

Ligand: 8 nM ^{3}H Haloperidol

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 4 hours at 25 °C

Incubation Buffer: 5 mM K_2HPO_4/KH_2P0_4 buffer pH 7.5

NonSpecific Ligand: 10 μM Haloperidol

K_d: 5.8nM*

B_{max}: 0.71 pmol/mg Protein*

Specific Binding: 80% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

23. Sigma σ_2 (Hashimoto and London, **1993**, *Eur. J. Pharmacol.* 236:159-163

Source: Wistar Rat brain

Ligand: 3 nM ^{3}H Ifenprodil

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 60 minutes at 37 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4

NonSpecific Ligand: 10 μM Ifenprodil

K_d: 4.8 nM*

B_{max}: 1.3 pmol/mg Protein *

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

24. Sodium Channel, Site 2 (Catterall *et al.*, **1981**, *J. Biol. Chem.* 256:8922-8927.

Source: Wistar Rat brain

Ligand: 1.5 nM $_3$H Batrachotoxinin A 20-μ-Benzoate

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 30 minutes at 37 °C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4 at 25°C, 50 mM Hepes, 130 mM choline-Cl, 5.4 mM KCI, 0.8 mM $MgSO_4.7H_20$, 5.5 mM glucose, 40 μg/ml LqTx

NonSpecific Ligand: 100 μM Veratridine

K_d: 0.013 μM *

B_{max}: 0.88 pmol/mg Protein *

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

25. Vascular Endothelial Growth Factor (VEGF) (Gitay-Goren *et al.*, *1996, J. Biol. Chem.* 271:5519-5523).

Source: Human umbilical vein endothelial cells

Ligand: 0.1 μM ^{125}I $VEGF_{165}$

Vehicle: 0.4 % DMSO

Incubation Time/Temp: 3 hours at 25 °C

Incubation Buffer: Buffer 1: M199 medium, 20% FBS, 100 U/ml penicillin and 100 μg/ml streptomycin, 4 mM L-glutamate, 15 mM Hepes, pH 7.4.

Buffer 2: Buffer 1 containing 1 μg/ml Heparmn and 0.1% gelatin

NonSpecific Ligand: 3 nM $VEGF_{165}$

K_d: 0.035 nM *

B_{max}: 8900 R/cell Receoptors/cell*

Specific Binding: 85% *

Quantitation Method: Radioligand Binding

Significance Criteria: ≥ 50% of max stimulation or inhibition

* Historical Values

6.31 Example 31: In Vivo Z-Chamber Study

The Z-chamber assay is a fibrin-based *in vivo* assay, wherein fibrin and thrombin are added through a port in a two-sided chamber sealed by a nylon mesh. The chamber is implanted in the subcutaneous space of an animal and harvested for evaluation. Fibrin matrices are formed in normal wound healing and are used by tumors to sustain growth, thus Z-chambers are designed to study, for example, angiogenesis, wound healing, and tumor growth. In addition, their design is useful, for example, in studies of localized gene expression, stem cell, adenoviral, and tissue generation.

The efficacy of **101** in an *in vivo* tumor model was examined by Z-chamber® (SRI, Menlo Park, CA) study. Each tumor chamber consisted of 150-160 µl cell suspension made by suspending 190 million cells in 20 ml fibrin (4 mg/ml). Following the introduction of cell suspension, 2 units of thrombin was added into each chamber and the mixture was allowed to gel for 5-7 minutes before implantation.

Rats were anesthetized with Nembutal (35 mg/kg). The skin of rats was surgically prepared with 70 % alcohol. Two incisions (approximately 2 cm in length) were made on the back, one over the mid vertebral and the other over the lower vertebral region. Pockets were made in the subcutaneous fascia lateral to the incisions by blunt dissection with the help of scissors, and the chambers were placed deep into these pockets. The incision wounds were later closed with an autoclip stapling device.

101 was dissolved in a 1 to 1 cremophor:ethanol solution and diluted 4 times with 5 % dextrose on water. Animals with tumor chambers were injected daily with 50 mg/kg 101 or 5 mg/kg taxol every other day as a positive control. Tumor chambers were harvested on day 16 post implantation. Chambers were cleared of all fascia, and tissue in each chamber was fixed in 10 % formalin, paraffin embedded and stained with hematoxylin and eosin. The tumor thickness was measured and compared to a negative control, i.e., chambers with no treatment, and the positive treatment. Four rats were used per each group. The results are summarized in Figure 14.

These studies demonstrate the efficacy of illustrative compounds of the invention in reducing tumor thickness in an *in vivo* model. Particularly, illustrative compounds of the invention are effective in modulating biological activities of Edg-4, for example, inhibiting cell proliferation in an *in vivo* model.

Finally, it should be noted that there are alternative ways of implementing the present invention. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

All publications and patents cited herein are incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. A method of modulating an Edg-4 receptor mediated biological activity comprising contacting a cell expressing the Edg-4 receptor with an amount of a modulator of the Edg-4 receptor sufficient to modulate the Edg-4 receptor mediated biological activity wherein the modulator is not a phospholipid.

2. A method of modulating an Edg-4 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of a modulator of the Edg-4 receptor wherein the modulator is not a phospholipid.

3. The method of Claim 1 or 2, wherein the modulator is an agonist.

4. The method of Claim 1 or 2, wherein the modulator is an antagonist.

5. The method of Claim 1 or 2, wherein the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

6. The method of Claim 1 or 2, wherein the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

7. The method of Claim 1 or 2, wherein the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

8. The method of Claim 1 or 2, wherein the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

9. The method of Claim 1 or 2, wherein the biological activity is cell proliferation.

10. The method of Claim 9, wherein the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

11. The method of Claim 9, wherein the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to other Edg receptors.

12. The method of Claim 9, wherein the modulator exhibits at least about 200 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

13. The method of Claim 9, wherein the modulator exhibits at least about 10 fold inhibitory selectivity for Edg-4 relative to Edg-2 and Edg-7 receptors.

14. The method of Claim 9, wherein cell proliferation leads to ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colon cancer or prostrate cancer.

15. The method of Claim 9, wherein cell proliferation is stimulated by LPA.

16. The method of Claim 1 or 2, wherein the biological activity is calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP formation, increasing the level of fatty acids, actin polymerization, apoptosis, angiogenesis, inhibition of wound healing, inflammation, expression of endogenous protein growth factors, cancer invasiveness, regulation of autoimmunity or atherogenesis.

17. The method of Claim 1 or 2 wherein the modulator binds to the Edg-4 receptor with a binding constant of at least about 1 μM.

18. The method of Claim 1 or 2 wherein the modulator binds to the Edg-4 receptor with a binding constant between about 1 μM and 100 nM.

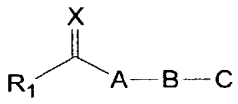
19. The method of Claim 1 or 2, wherein the modulator is a nucleic acid, peptide or carbohydrate.

20. The method of Claim 1 or 2, wherein the modulator is an organic molecule of molecular weight of less than 750 daltons.

21. The method of Claim 1, wherein the cell is a HTC hepatoma cell, an ovarian cell, an epithelial cell, a fibroblast cell, a neuronal cell, a *Xenopus laevis* oocyte cell, a carcinoma cell, a pheochromocytoma cell, a myoblast cell, a platelet cell or a fibrosarcoma cell.

22. The method of Claim 21, wherein the cell is 0V202 human ovarian cell, a HTC rat hepatoma cell, SKOV3 and CAOV-3 human ovarian cancer cells, MDA-MB-453 breast cancer cell, MDA-MB-23 1 breast cancer cell, HUVEC cells A43 1 human epitheloid carcinoma cell or a HT-1 080 human fibrosarcoma cell.

23. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (I):



(I)

or a pharmaceutically available solvate or hydrate thereof, wherein:

R_1 is hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkylarylamino, substituted alkylarylamino, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylamino, substituted arylamino, arylalkyl, substituted arylalkyl, dialkylamino, substituted dialkylamino, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl sulfonylamino or substituted sulfonylamino;

X=0 or S;

A is NR_2, 0 or S;

R_2 is hydrogen, alkyl or substituted alkyl; and

B and C are independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

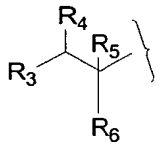
24. The method of Claim 23, wherein R_1 is alkyl, substituted alkyl, aryl, substituted aryl, arylalkyloxy or substituted sulfonylamino.

25. The method of Claim 23, wherein R_1 is substituted alkyl.

26. The method of Claim 23, wherein R_1 is substituted haloalkyl.

27. The method of Claim 23, wherein R_1 is substituted trifluoroalkyl.

28. The method of Claim 23, wherein R_1 has the structural formula (II):



(II)

wherein:

R_3 is haloalkyl or substituted haloalkyl;

R_4 is oxo or thiono; and

R_5 and R_6 are independently hydrogen, halo, alkyl or substituted alkyl.

29. The method of Claim 28, wherein R_3 is fluoroalkyl, R_4 is oxo and R_5 and R_6 are independently hydrogen, halo or alkyl.

30. The method of Claim 28, wherein R_3 is trifluoromethyl, R_4 is oxo and R_5 and R_6 are independently hydrogen, chloro or methyl.

31. The method of Claim 28, wherein R_5 and R_6 are hydrogen.

32. The method of Claim 28 wherein R_5 is hydrogen and R_6 is chloro or methyl.

33. The method of Claim 23, 28 or 30 wherein X is 0, A is NR_2 and R_2 is hydrogen.

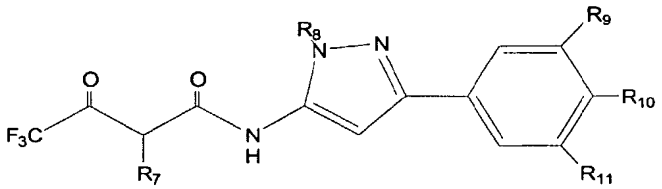
34. The method of Claim 23, 28 or 30 wherein B and C are independently, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

35. The method of Claim 23, 28 or 30 wherein B and C are independently indolo, substituted indolo, imidazolo, substituted, imidazolo, pyrazolo, substituted pyrazolo, phenyl or substituted phenyl.

36. The method of Claim 23, 28 or 30 wherein B is heteroaryl or substituted heteroaryl and C is aryl or substituted aryl.

37. The method of Claim 23, 28 or 30 wherein B is pyrazolo or substituted pyrazolo and C is phenyl or substituted phenyl.

38. The method of Claim 23, wherein the modulator is a compound of structural formula (III):



(III)

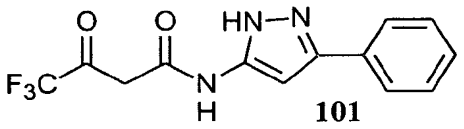
wherein:

R_7 is hydrogen, alkyl, substituted alkyl or halo;

R_8 is hydrogen, carbamoyl or substituted carbamoyl; and

R_9, R_{10} and R_{11} are independently hydrogen, alkoxy, substituted alkoxy, halo or $P._9$ and $P._{10}$ together with the carbons to which they are attached form a [1,3] dioxolane ring.

39. The method of Claim 23, wherein the modulator is compound of the formula:



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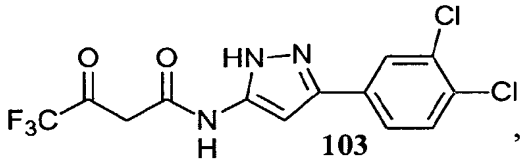

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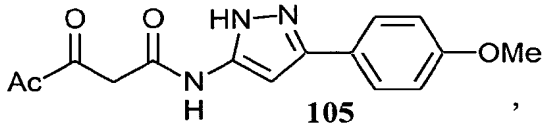

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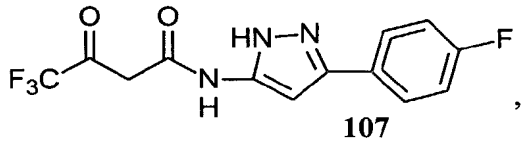

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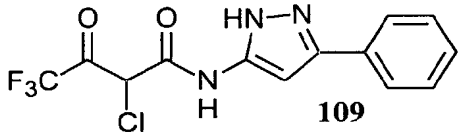

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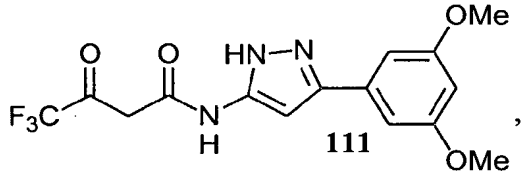

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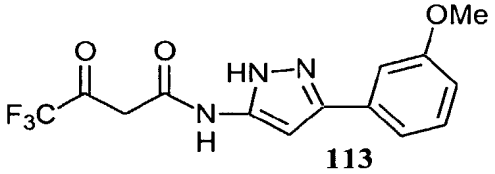

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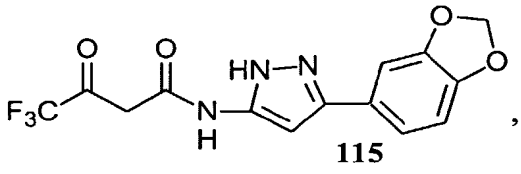

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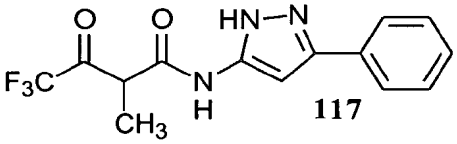

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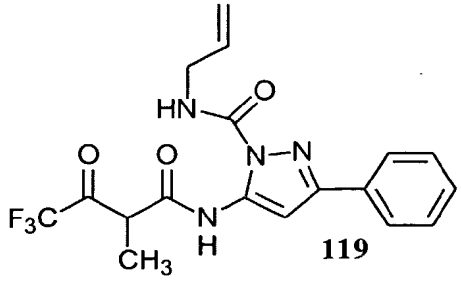

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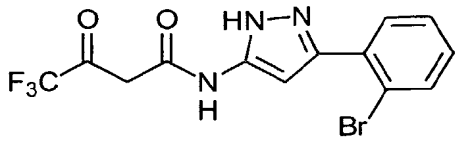

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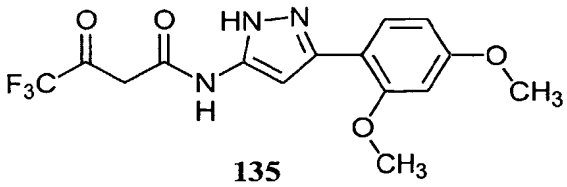

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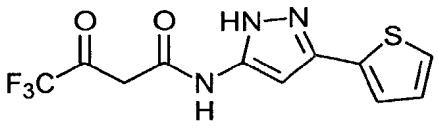

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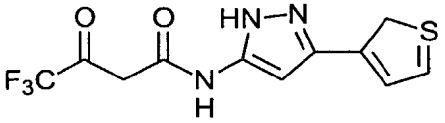
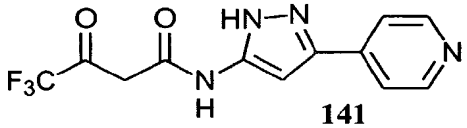


139

or

,



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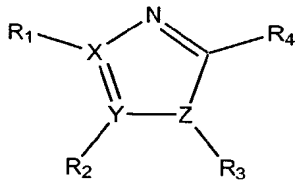
40. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (IV):

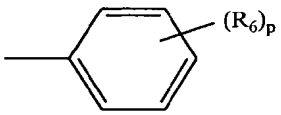


(IV)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, $-(C_5-C_{10})$cycloheteroaryl, $-(C_3-C_6)$cycloheteroalkyl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-NR_5R_5$, $=NR_5$,

$-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_3-C_{10})cycloheteroalkyl(R_5)_m$, $-(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X and Y are each independently C or N; and

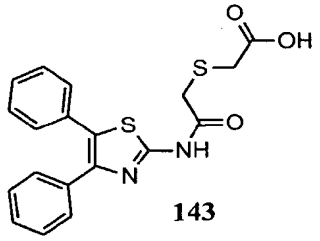
Z is O, S, C or N, wherein if Z is O or S, then R_3 is an electron pair;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_3 and R_4 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

41. The method of Claim 40, wherein the modulator is a compound of the following formula:



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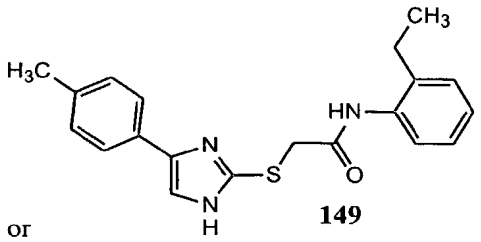
, or



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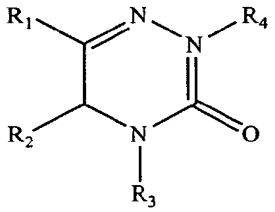
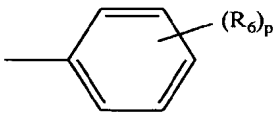
42. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (V):



(V)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

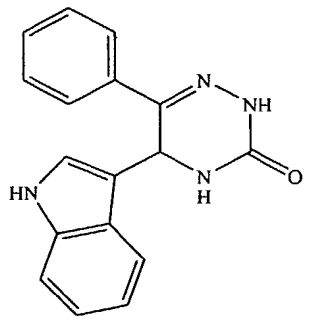
each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl,

-C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;
m is independently an integer ranging from 0 to 8;
p is independently an integer ranging from 0 to 5; and
R_1 and R_2 or R_2 and R_3 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

43. The method of Claim 42, wherein R_1 and R_2 are independently aryl, substituted aryl, heteroaryl or substituted heteroaryl.

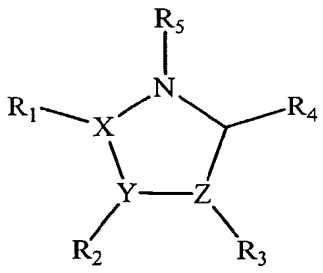
44. The method of Claim 42, wherein R_2 is indole and R_3 and R_4 are hydrogen.

45. The method of Claim 42, wherein the modulator is a compound of the following formula:



or its (+) and (-) enantiomers.

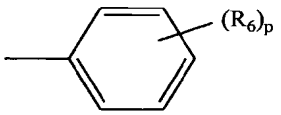
46. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (VI):



(VI)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4 or R_5 is independently -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

X, Y and Z are independently O, S, C or N, wherein if X, Y or Z is O or S, R_1 is an electron pair;

R_1 and R_2 or can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring;
R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;
R_1 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and
R_4 and R_5 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

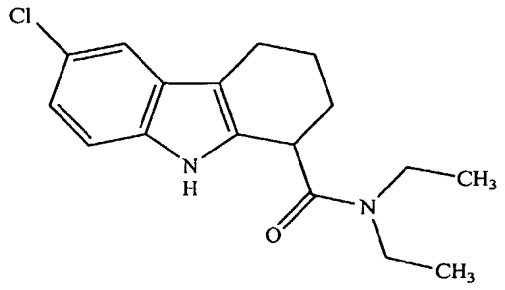
47. The method of Claim 46, wherein R_1 and R_2 together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

48. The method of Claim 46, wherein: R_1 and R_2 together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and R_3 and R_4 together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

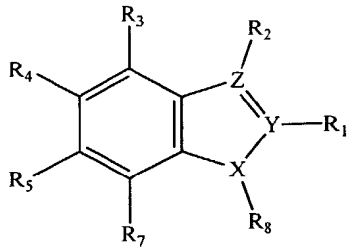
49. The method of Claim 46, wherein: R_1 and R_2 together form a 6- membered substituted or unsubstituted cyclic or aromatic ring; and R_3 and R_4 together form a 6-membered substituted or unsubstituted cyclic or aromatic ring.

50. The method of Claim 46, wherein: R_1 and R_2 form a 6-membered substituted cyclic or aromatic ring, and R_3 and R_4 form a 6-membered substituted cyclic or aromatic ring.

51. The method of Claim 46, wherein the modulator is a compound of the following formula:



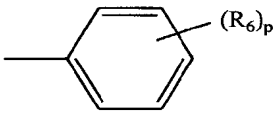
52. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (VII):



(VII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

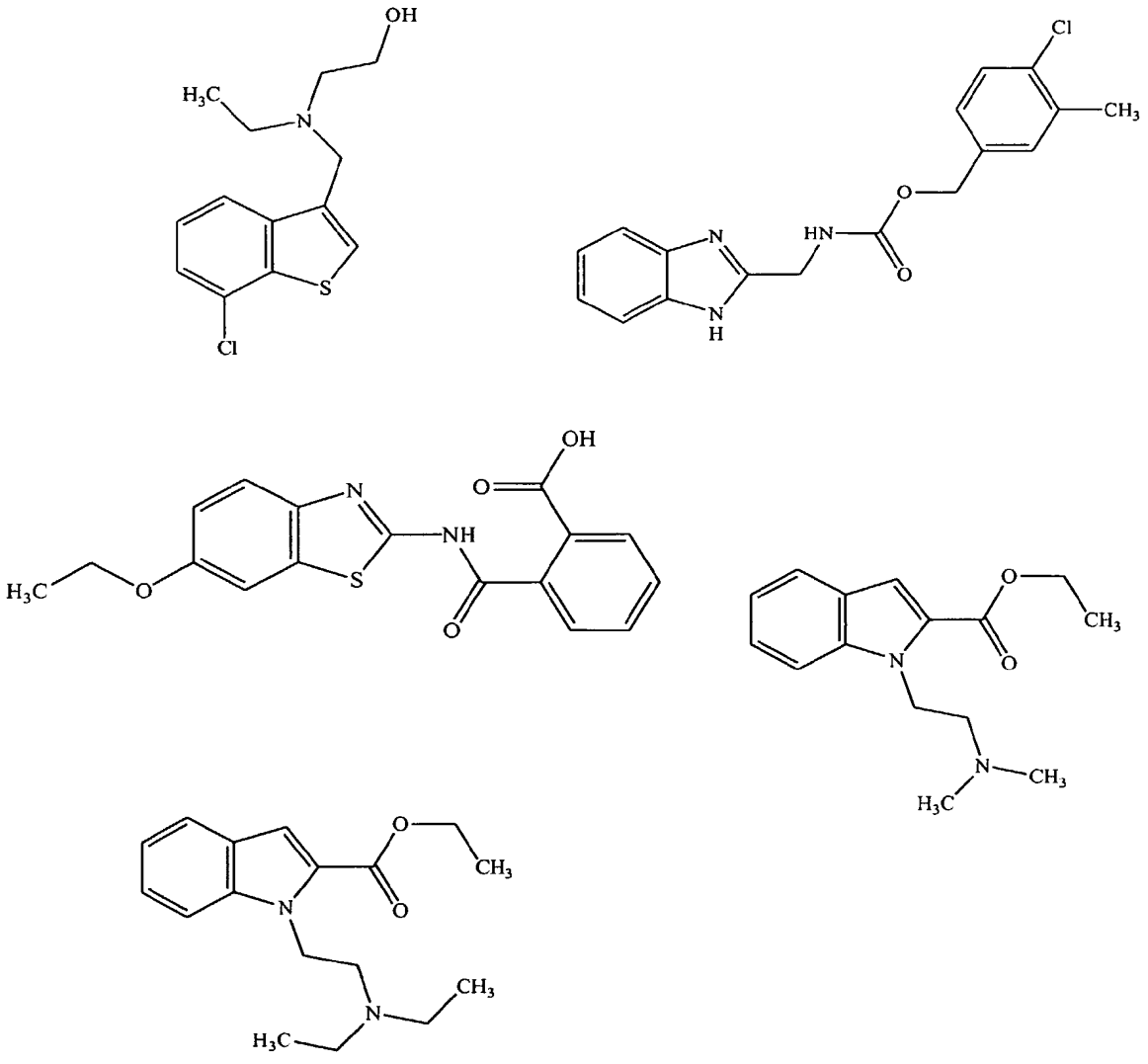
m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

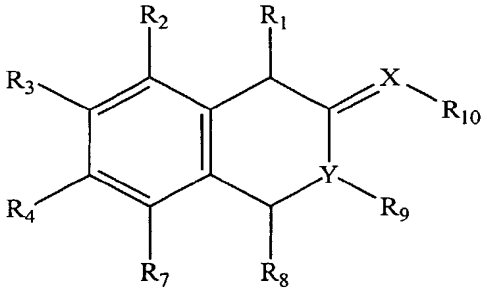
X is O, S, C or N, wherein if X is O or S, R_1 is an electron pair; and

Y and Z are independently N or C, wherein if Y or Z is N, R_1 and R_2 are each an electron pair.

53. The method of Claim 52, wherein the modulator is a compound of the following formula:



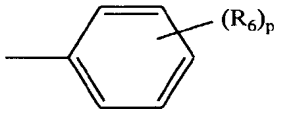
54. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (VIII):



(VIII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

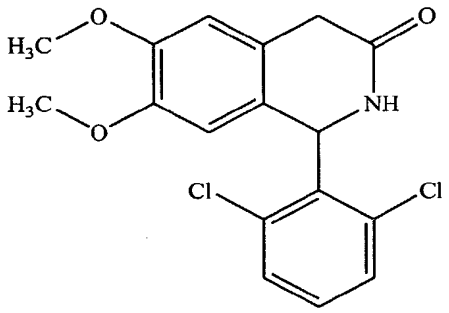
m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5; and

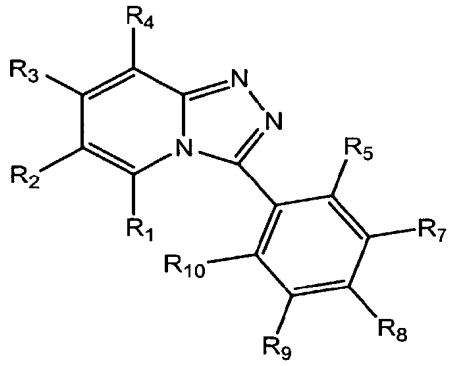
X and Y are independently O, S or N, wherein if X or Y is O or S, R_9 and R_{10} are an electron pair.

55. The method of Claim 54, wherein R_7 is substituted or unsubstituted aryl.

56. The method of Claim 54, wherein the modulator is a compound of the following formula:



57. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (IX):

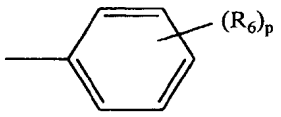


(IX)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9 or R_{10} is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$,

$-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

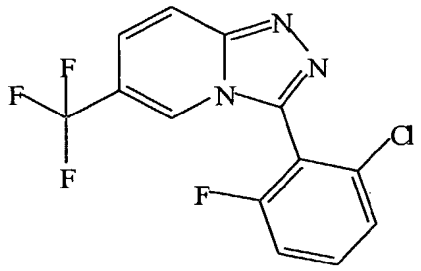
each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;
m is independently an integer ranging from 0 to 8; and
p is independently an integer ranging from 0 to 5.

58. The method of Claim 57, wherein R_2 is a substituted alkyl, and one or more of R_5, R_7, R_8, R_9 and R_{10} are halos.

58. The method of Claim 57, wherein R_2 is a halo-substituted alkyl.

59. The method of Claim 57, wherein R_2 is $-CF_3$.

60. The method of Claim 57, wherein the modulator is a compound of the following formula:



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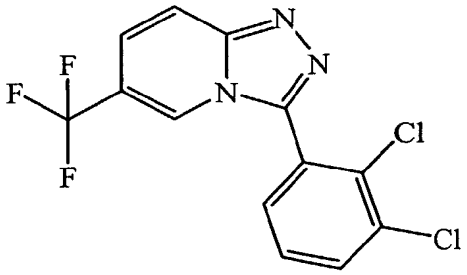
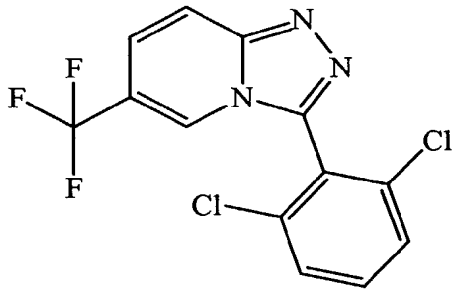


129



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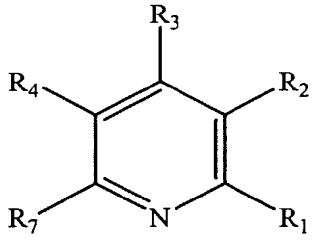
61. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (X):

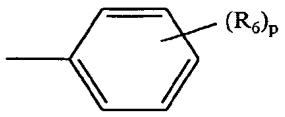


(X)

10 or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl,

-(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -(C_5-C_{10})heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -(C_1-C_{10})alkylNHC(O)$(CH_2)_mR_5$, -(C_1-C_{10})alkylNR_5R_5, $-CO_2H$, -(C_1-C_{10})alkylC(O)$NH(CH_2)_mR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, -N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)$NH(CH_2)_m$(C_1-C_{10})alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH$((C_1-C_{10})alkyl(C_1-C_{10})alkyl), $-CO_2$(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, $-CO_2(CH_2)_m$(C_1-C_{10})alkyl, $-CO_2(CH_2)_mH$, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

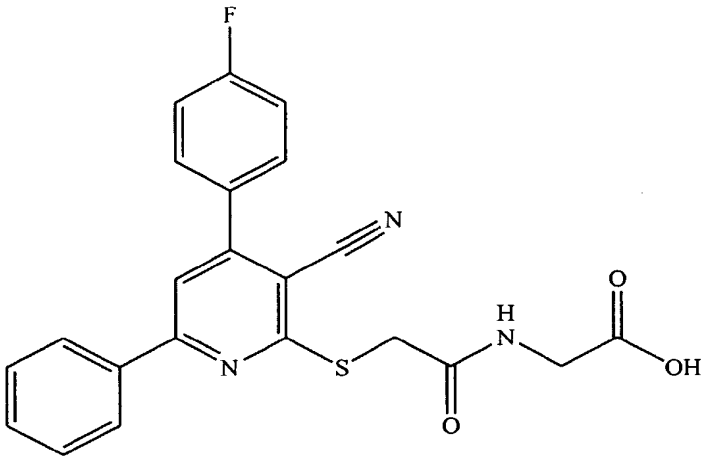
R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

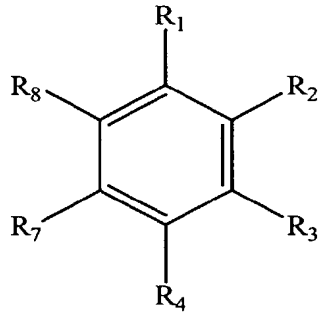
R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

62. The method of Claim 61, wherein R_3 and R_7 are substituted or unsubstituted aryls.

63. The method of Claim 61, wherein the modulator is a compound of the following formula:



64. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (XI):

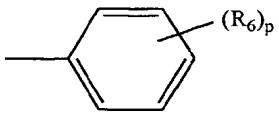


(XI)

or a pharmaceutically available solvate or hydrate thereof, wherein:

each of R_1, R_2, R_3, R_4, R_5, R_7 or R_8 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, $-(C_5-C_{10})$cycloheteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$,

$-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

m is independently an integer ranging from 0 to 8;

p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_2 and R_3 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_3 and R_4 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

R_4 and R_7 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring;

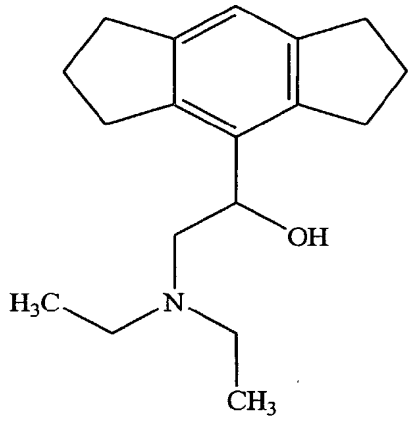
R_7 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and R_8 can optionally together form a 5-, 6- or 7-membered substituted or unsubstituted cyclic or aromatic ring.

65. The method of Claim 64, wherein R_2 and R_3 together form a 5-membered ring.

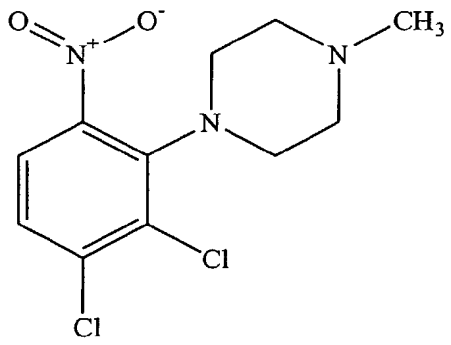
66. The method of Claim 64, wherein R_2 and R_3 together form a 5-membered ring, and R_7 and R_8 together form a 5-membered ring.

67. The method of Claim 64, wherein the modulator is a compound of the following formula:

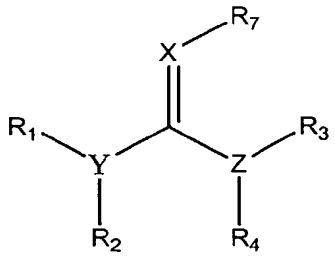


68. The method of Claim 64, wherein R_2 is a substituted or unsubstituted piperazine moiety.

69. The method of Claim 64, wherein the modulator is a compound of the following formula:



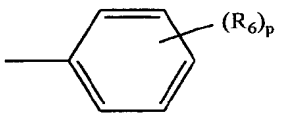
70. The method of Claim 1 or 2, wherein the modulator is a compound of structural formula (XII):



(XII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3, R_4, R_5 or R_7 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-(CH_2)_mN(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-C(OH)R_5$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, $-(C_5-C_{10})$cycloheteroaryl, $-(C_3-C_6)$cycloheteroalkyl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-NR_5R_5$, $=NR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_3-C_{10})$cycloheteroalkyl$(R_5)_m$, $-(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 or R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl,

-(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -$CO_2(CH_2)_m$(C_1-C_{10})alkyl, -$CO_2(CH_2)_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

m is independently an integer ranging from 0 to 8;

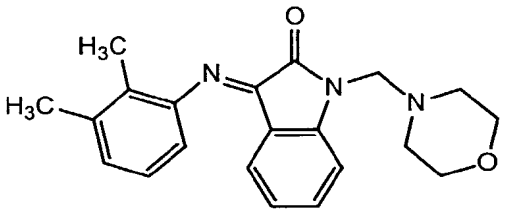
p is independently an integer ranging from 0 to 5;

R_3 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring;

R_1 or R_2 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring; and

R_2 or R_4 can optionally form a substituted or unsubstituted cyclic, aromatic, heterocyclic, heteroaryl or cycloheteroalkyl ring.

71. The method of Claim 70, wherein the modulator is a compound of the following formula:



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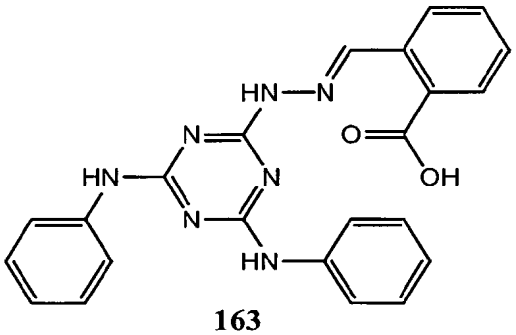

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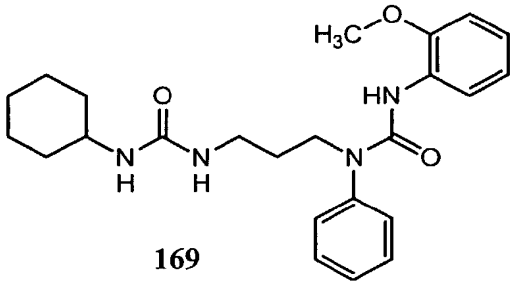
or



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72. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (I)-(XII).

73. A method for treating or preventing ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, adult respiratory distress syndrome (ARDS), asthma, transcomeal freezing, cutaneous bums, ischemia or arthesclerosis in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (I)-(XII).

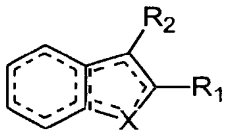
74. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (I)-(XII) and one or more agonists or antagonists of an LPA receptor.

75. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (I)-(XII) and one or more drugs useful in treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases.

76. A method of modulating an Edg-7 receptor mediated biological activity comprising contacting a cell expressing the Edg-7 receptor with an amount of a modulator of the Edg-7 receptor sufficient to modulate the Edg-7 receptor mediated biological activity wherein the modulator is not a phospholipid.

77. A method of modulating an Edg-7 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of an modulator of the Edg-7 receptor wherein the modulator is not a phospholipid.

78. The method of Claim 76 or 77, wherein the modulator is a compound of structural formula (XIII):



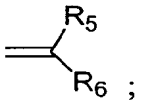
(XIII)

or a pharmaceutically available solvate or hydrate thereof, wherein:

X is NR^3, S or O;

R_1 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, amino, carbamoyl, substituted carbamoyl, oxo, thiono or $-NR^4$; and

R_2 is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkyloxy, substituted alkyloxy, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, amino, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or



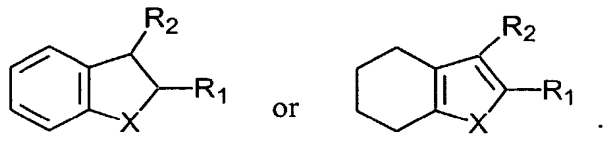
;

R_3 is hydrogen, alkyl, substituted alkyl, alkylthio, substituted alkylthio, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl or substituted heteroalkyl;

R_4 is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heteroaryl substituted heteroaryl, cycloheteroalkyl, substituted cycloheteroalkyl, and

R_5 and R_6 are independently hydrogen, alkyl, substituted alkyl, acylamino, substituted acylamino, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, alkylsulfonyl, substituted alkylsulfonyl, alkylsulfinyl, substituted alkylsulfinyl, arylalkyloxy, substituted arylalkyloxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl or optionally along with the carbon to which they are attached form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

79. The method of Claim 78, wherein the modulator is a compound according to the structural formula:



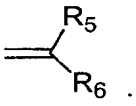
80. The method of Claim 78, wherein X is S or NR_3.

81. The method of Claim 78, wherein R_1 is oxo, thiono or NR_4.

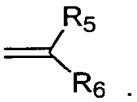
82. The method of Claim 81, where R_4 is acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, carbamoyl or substituted carbamoyl.

83. The method of Claim 81, where R_4 is substituted carbamoyl..

84. The method of Claim 78, wherein R_2 is acyl, substituted acyl, acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, alkylsulfonyl, substituted alkylsulfonyl, aryloxycarbonyl, substituted aryloxycarbonyl, carbamoyl, substituted carbamoyl, or



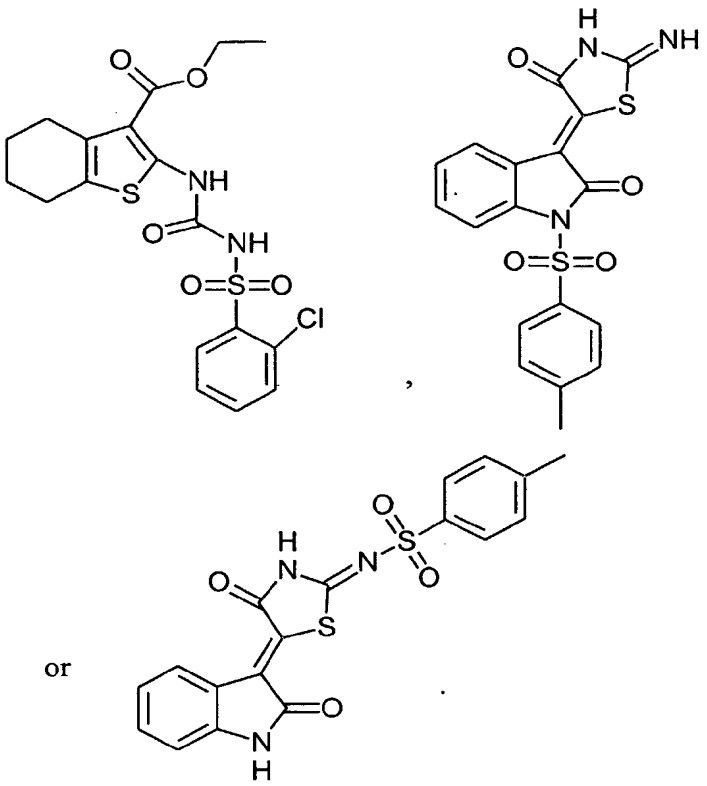
85. The method of Claim 78, wherein R_2 is substituted alkoxycarbonyl or



86. The method of Claim 85, where R_5 and R_6 along with the carbon to which they are attached form a cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

87. The method of Claim 85, where R_5 and R_6 along with the carbon to which they are attached form a substituted cycloheteroalkyl ring.

88. The method of Claim 78, wherein the modulator is compound of the formula:



or

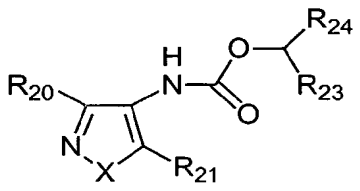
89. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XIII).

90. A method for treating or preventing ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, adult respiratory distress syndrome (ARDS), asthma, transcorneal freezing, cutaneous burns, ischemia or arthesclerosis in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XIII).

91. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XIII).

92. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XIII), and one or more drugs useful in treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases.

93. A method of modulating an Edg-2 receptor mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an amount of an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor mediated biological activity wherein the modulator is not a lipid, phospholipid or a compound of the structural formula:



or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

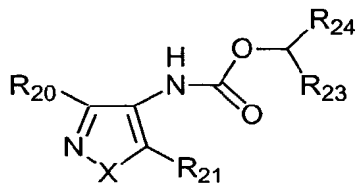
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

or alternatively R_{23} and R_{24} from a cycloalkyl ring.

94. A method of modulating an Edg-2 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of an modulator of the Edg-2 receptor wherein the modulator is not a phospholipid wherein the modulator is not a lipid, a phospholipid or a compound of the structural formula (I):



or a pharmaceutically available salt thereof, wherein:

X is O or S;

R_{20} is alkyl, substituted alkyl, aryl, substituted aryl or halo;

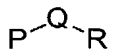
R_{21} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{23} is hydrogen, alkyl or substituted alkyl;

R_{24} is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

or alternatively R_{23} and R_{24} from a cycloalkyl ring.

95. The method of Claim 93 or 94 wherein the modulator is a compound of structural formula (XXII):

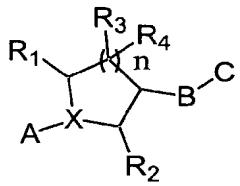


(XXII)

or a pharmaceutically available salt, hydrate or solvate thereof wherein:

P, Q and R are independently aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl.

96. The method of Claim 95 wherein the modulator is a compound of structural formula (XXIII):



(XXIII)

wherein:

n is 1, 2 or 3;

X = N or CH;

R_1 and R_2 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cyano, cyanato, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxo or thiono;

R_3 and R_4 are independently hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, halo or thio;

B is NR_5, O or S;

R_5 is hydrogen, alkyl, substituted alkyl, alkylamino, substituted alkylamino, alkoxy, substituted alkoxy, amino, cyano, dialkylamino, substituted dialkylamino or hydroxy; and

A and C are independently aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl.

97. The method of Claim 96, wherein R_1 and R_2 are independently hydrogen, alkyl substituted alkyl, oxo or thiono.

98. The method of Claim 96, wherein R_1 and R_2 are independently oxo or thiono.

99. The method of Claim 96, wherein R_3 and R_4 are independently hydrogen or alkyl.

100. The method of Claim 96, wherein A and C are independently aryl, substituted aryl, heteroaryl or substituted heteroaryl.

101. The method of Claim 96, wherein A and C are aryl or substituted aryl.

102. The method of Claim 96, wherein A and C are phenyl or substituted phenyl.

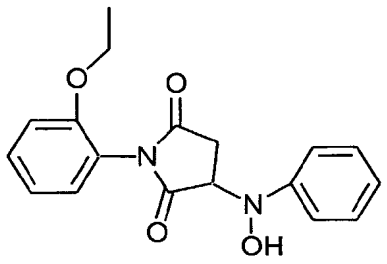
103. The method of Claim 96, wherein B is NR_5 and R_5 is hydrogen, alkyl or hydroxy.

104. The method of Claim 96, wherein n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5 and R_5 is hydroxy.

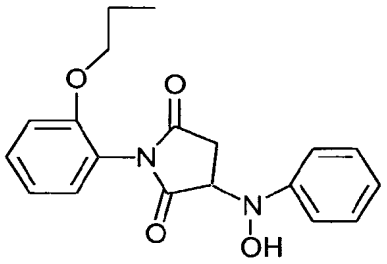
105. The method of Claim 96, wherein n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5, R_5 is hydroxy, A and B are aryl or substituted aryl.

106. The method of Claim 96, wherein n is 1, R_1 and R_2 are oxo, R_3 and R_4 are hydrogen, B is NR_5, R_5 is hydroxy, A and B are phenyl or substituted phenyl.

107. The method of Claim 96, wherein the modulator has the formula:



or



.

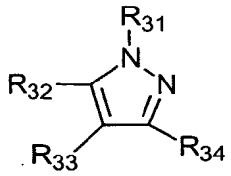
108. The method of Claim 95, wherein Q is cycloheteroalkyl, substituted cycloheteroalkyl and P and R are independently aryl or substituted aryl.

109. The method of Claim 95, wherein Q is cycloheteroalkyl or substituted cycloheteroalkyl and P and R are independently phenyl or substituted phenyl.

110. The method of Claim 95, wherein Q is heteroaryl or substituted heteroaryl and P and R are independently aryl or substituted aryl.

111. The method of Claim 95, wherein Q is heteroaryl or substituted heteroaryl and P and R are independently phenyl or substituted phenyl.

112. The method of Claim 95, wherein the modulator has the structural formula (XXIV):



(XXIV)

wherein:

R_{31} is hydrogen, alkyl or substituted alkyl;

R_{32} is hydrogen, alkyl or substituted alkyl;

R_{33} is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_{34} is aryl, substituted aryl, heteroaryl or substituted heteroaryl.

113. The method of Claim 112, wherein R_{31} and R_{32} are alkyl.

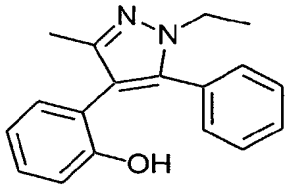
114. The method of Claim 112, wherein R_{33} and R_{34} are aryl or substituted aryl.

115. The method of Claim 112, wherein R_{31} and R_{32} are alkyl and R_{33} and R_{34} are aryl or substituted aryl.

116. The method of Claim 112,wherein R_{33} and R_{34} are phenyl or substituted phenyl.

117. The method of Claim 112, wherein R_{31} and R_{32} are methyl or ethyl and R_{33} and R_{34} are phenyl or substituted phenyl.

118. The method of Claim 95, wherein the modulator has the formula:



119. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXIII) or (XXIV).

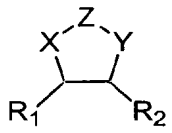
120. A method for treating or preventing ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, adult respiratory distress syndrome (ARDS), asthma, transcorneal freezing, cutaneous burns, ischemia or arthesclerosis in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXIII) or (XXIV).

121. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXIII) or (XXIV) and one or more agonists or antagonists of an Edg-2 receptor.

122. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXIII) or (XXIV) and one or more drugs useful in treating or

preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases.

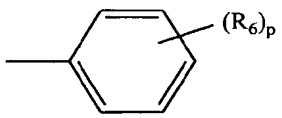
123. A method of modulating an Edg-2 receptor mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an amount of an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor mediated biological activity wherein the modulator is of the structural formula (XXII):



(XXII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, -

OCF_3, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

X, Y, and Z are each independently $C(R_5)(R_5)$, C(O), O, C(S), S, $C=N(R_5)$, or NR_3;

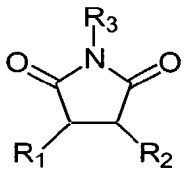
each m is independently an integer ranging from 0 to 8;

each p is independently an integer ranging from 0 to 5;

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring; and

R_1 and X or R_2 and Y can together form a double bond.

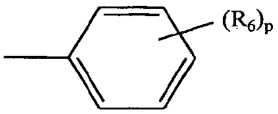
124. A method of modulating an Edg-2 receptor mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an amount of an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor mediated biological activity wherein the modulator has the structural formula (XXIII):



(XXIII)

wherein:

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, $-(C_5-C_{10})heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-(C_1-C_{10})alkylNHC(O)(CH_2)_mR_5$, $-(C_1-C_{10})alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

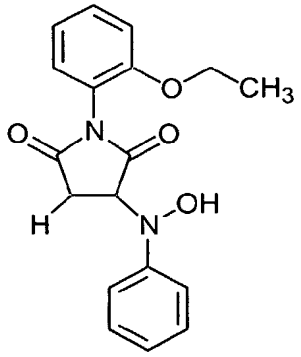
each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

each m is independently an integer ranging from 0 to 8;

each p is independently an integer ranging from 0 to 5; and

R_1 and R_2 can optionally together form a 5-, 6-, or 7-membered substituted or unsubstituted cyclic or aromatic ring.

125. The method of Claim 123 or 124 wherein the modulator is a compound of structural formula:



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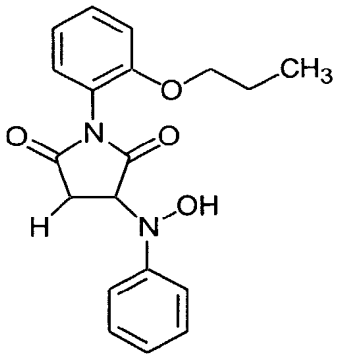
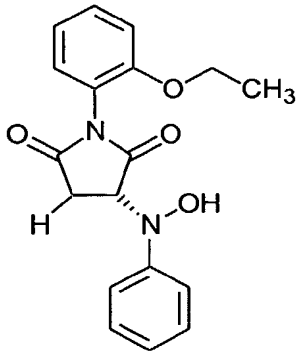
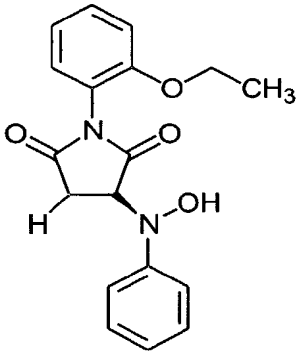


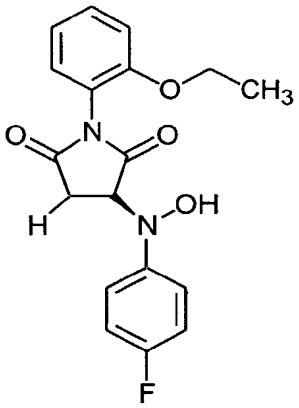
205



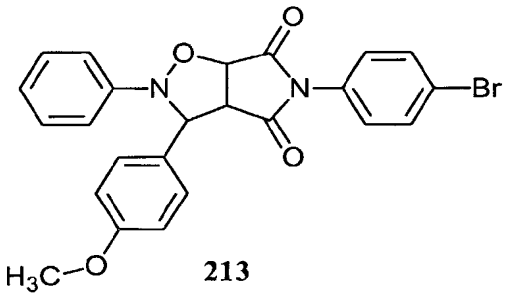
207



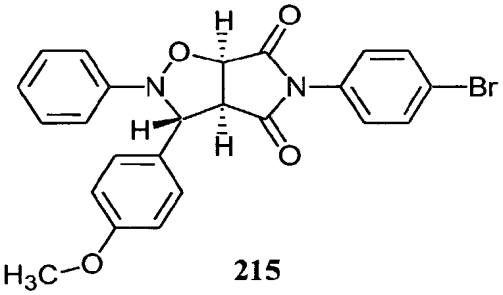
209



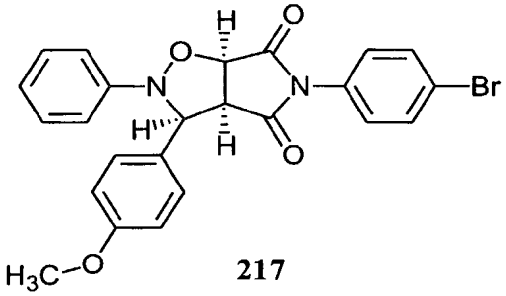
211



213



215



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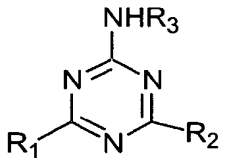
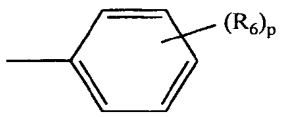
126. A method of modulating an Edg-2 receptor mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an amount of an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor mediated biological activity wherein compound of the structural formula (XXI):



(XXI)

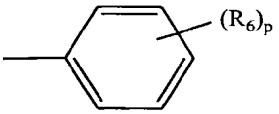
or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, -OC(O)aryl, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5,

$-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



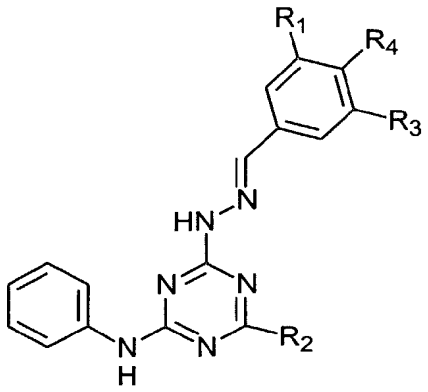
wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

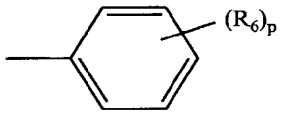
127. A method of modulating an Edg-2 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of an modulator of the Edg-2 receptor wherein the modulator a compound of the structural formula (XXII):



(XXII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_4 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -OCF_3, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -heterocylcoalkyl, -$OC(O)$aryl, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



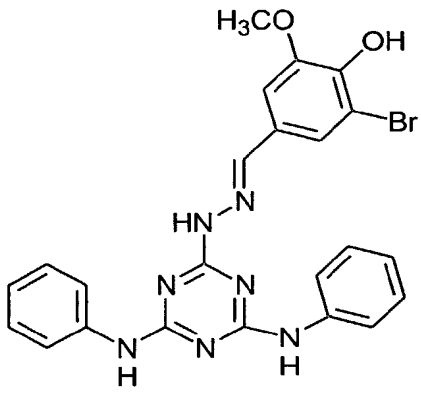
wherein;

each R_5 and R_6 is independently -halo, -NO_2, -CN, -OH, -CO_2H, -$N(C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl, -$O(C_1$-$C_{10})$alkyl, -$C(O)(C_1$-$C_{10})$alkyl, -$C(O)NH(CH_2)_m(C_1$-$C_{10})$alkyl, -OCF_3, -benzyl, -$CO_2(CH_2)_mCH((C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl), -$CO_2(C_1$-$C_{10})$alkyl, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, -$CO_2(CH_2)_mH$, -$NHC(O)(C_1$-$C_{10})$alkyl, -$NHC(O)NH(C_1$-$C_{10})$alkyl, -NH(aryl), -N=C(aryl), -$OC(O)O(C_1$-$C_{10})$alkyl, or -SO_2NH_2;

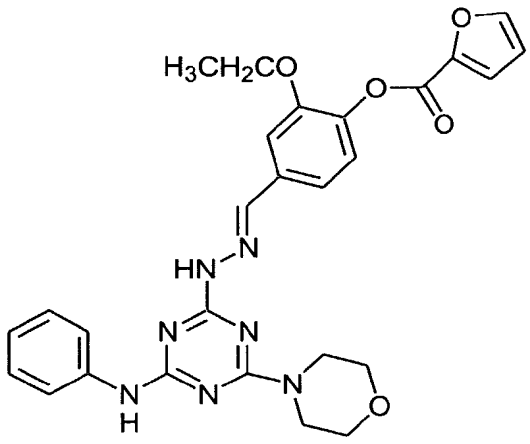
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

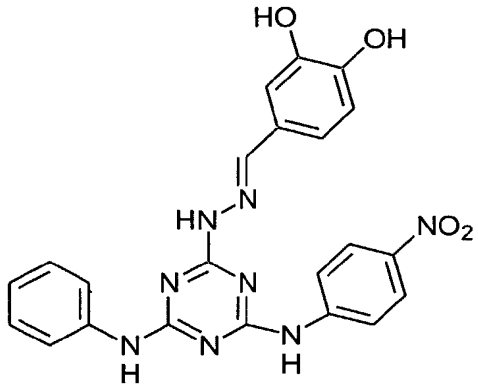
128. The method of Claim 95 wherein the modulator is a compound selected from the group consisting of:



227



229



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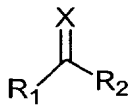
129. A method of modulating an Edg-2 receptor mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an amount of

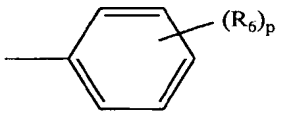
an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor mediated biological activity wherein compound of the structural formula (XXI):



(XXI)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1 and R_2 is independently -H, -halo, -NO_2, -CN, -$C(R_5)_3$, -$(CH_2)_mOH$, -$N(R_5)(R_5)$, -$O(CH_2)_mR_5$, -$C(O)R_5$, -$C(O)NR_5R_5$, -$C(O)NH(CH_2)_m(R_5)$, -OCF_3, -NH(aryl), -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -aryl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_3$-$C_{10})$cycloalkyl(aryl), -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -N(OH)aryl, -$NHC(O)R_5$, -$NHC(O)OR_5$, -$NHC(O)NHR_5$, -heterocylcoalkyl, -$(C_1$-$C_{10})$alkylNHC$(O)(CH_2)_mR_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -$OC(O)(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$, -$OC(O)OR_5$, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, -NO_2, -CN, -OH, -CO_2H, -$N(C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl, -$O(C_1$-$C_{10})$alkyl, -$C(O)(C_1$-$C_{10})$alkyl, -$C(O)NH(CH_2)_m(C_1$-$C_{10})$alkyl, -OCF_3, -benzyl, -$CO_2(CH_2)_mCH((C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl), -$CO_2(C_1$-$C_{10})$alkyl, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, -$CO_2(CH_2)_mH$, -$NHC(O)(C_1$-$C_{10})$alkyl, -$NHC(O)NH(C_1$-$C_{10})$alkyl, -NH(aryl), -N=C(aryl), -$OC(O)O(C_1$-$C_{10})$alkyl, or -SO_2NH_2;

X is O, S, Or NR_6;

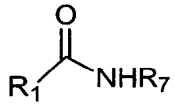
R_1 and R_2 can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

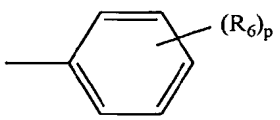
130. A method of modulating an Edg-2 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of an modulator of the Edg-2 receptor wherein the modulator a compound of the structural formula (XXII):



(XXII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

R_1 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5\text{-}C_{10})$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-OC(O)$aryl, $-(C_1\text{-}C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1\text{-}C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

R_7 is $-CO_2H$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$;

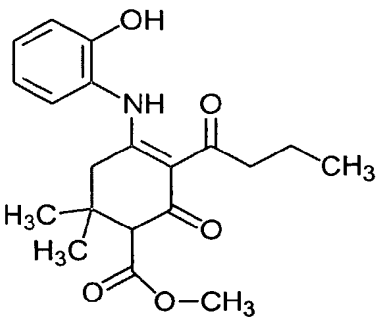
R_1 and R_2 can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

131. The method of Claim 95 wherein the modulator is a selected from the group consisting of:



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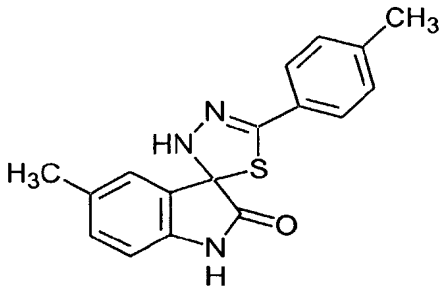
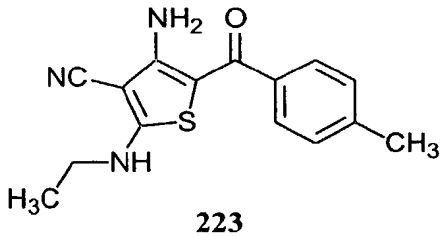
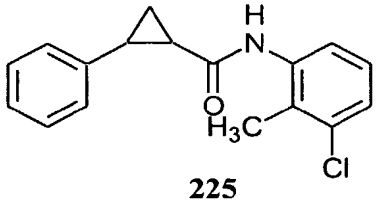


221



223

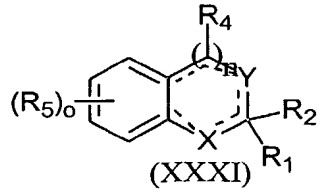


225

132. A method of modulating an Edg-3 receptor mediated biological activity comprising contacting a cell expressing the Edg-3 receptor with an amount of an modulator of the Edg-3 receptor sufficient to modulate the Edg-3 receptor mediated biological activity wherein the modulator is not a phospholipid.

133. A method of modulating an Edg-3 receptor mediated biological activity in a subject comprising administering to the subject a therapeutically effective amount of an modulator of the Edg-3 receptor wherein the modulator is not a phospholipid.

134. The method of Claim 132 or 133, wherein the modulator is a compound of structural formula (XXXI):



(XXXI)

or a pharmaceutically available solvate or hydrate thereof, wherein:

n = 0 or 1;

o is 0, 1, 2, 3 or 4;

X is C, NR^7 O or S;

Y is C, NR^8 O or S;

R_1 is either absent or hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

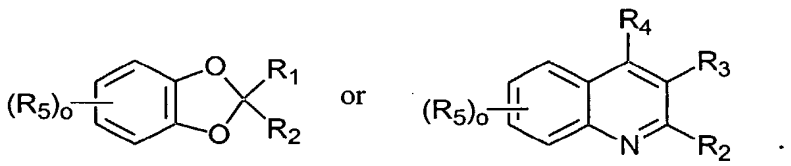
R_2, R_3 and R_4 are independently hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl;

each R_5 is independently, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted

alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro or thio; and

$R_7$and R_8 are independently absent, hydrogen, alkyl, substituted alkyl, acyl or substituted acyl.

135. The method of Claim 134, wherein the modulator is a compound of structural formula (XXXV) or (XXXVI):



(XXXV) (XXXVI)

136. The method of Claim 135, wherein R_1 is either absent or hydrogen, acyl, substituted acyl, acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, arylalkyloxy, substituted arylalkyloxy, carbamoyl, substituted carbamoyl, dialkylamino, substituted dialkylamino, heteroalkyl, or substituted heteroalkyl.

137. The method of Claim 134, wherein R_1 is either absent or acylamino, substituted acylamino, alkoxycarbonyl, substituted alkoxycarbonyl, arylamino substituted arylamino, or carbamoyl, substituted carbamoyl.

138. The method of Claim 134, wherein R_1 is either absent or acylamino, substituted acylamino, arylamino or substituted arylamino.

139. The method of Claim 134, wherein R_2, R_3 and R_4 are independently alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, carbamoyl, substituted carbamoyl, dialkylamino, substituted dialkylamino, heteroaryl, substituted heteroaryl, heteroalkyl, or substituted heteroalkyl.

140. The method of Claim 134, wherein R_2, R_3 and R_4 are independently alkyl, substituted alkyl, acylamino, substituted acylamino, aryl, substituted aryl, arylamino, substituted arylamino, carbamoyl or substituted carbamoyl.

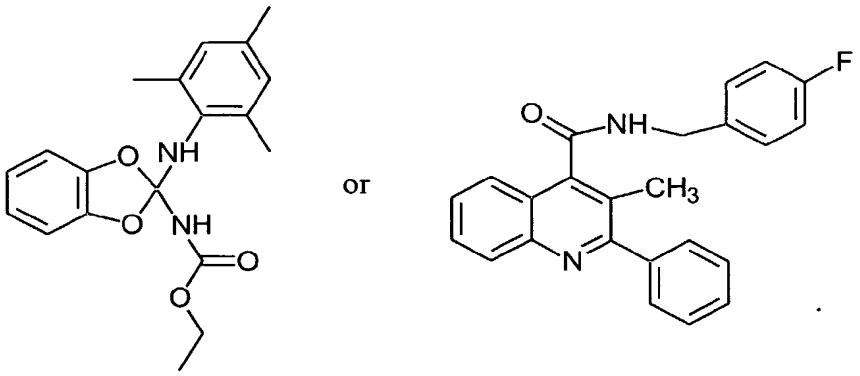
141. The method of Claim 134, wherein R_2, R_3 and R_4 are independently alkyl, substituted acylamino, aryl, substituted arylamino or substituted carbamoyl.

142. The method of Claim 134, wherein each R_5 is independently, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, amino, aryl, substituted aryl, azido, carboxy, carbamoyl, substituted carbamoyl, cyano, halo, hydroxyl, nitro or thio.

143. The method of Claim 134, wherein each R_5 is independently, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, azido, carboxy, carbamoyl, substituted carbamoyl, cyano, halo, hydroxyl, nitro or thio.

144. The method of Claim 134, wherein $R_7$and R_8 are independently absent, hydrogen, alkyl.

145. The method of Claim 134, wherein the modulator is a compound of the formula:



146. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, or cardiovascular diseases in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI).

147. A method for treating or preventing ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer, breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid cancer, lung cancer, kidney cancer, pancreas cancer, prostrate cancer, adult respiratory distress syndrome (ARDS), asthma, transcorneal freezing, cutaneous burns, ischemia or arthesclerosis in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI).

148. A method for treating or preventing vasoconstriction, autoimmune disorders or vascular occlusive disorders in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI).

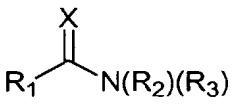
149. A method for treating or preventing vasoconstriction in cerebral arteries, systemic lupus erythematosus (SLE), rheumatoid arthritis, non-glomerular nephrosis, psoriasis, chronic active hepatitis, ulcerative colitis, Crohn's disease, Behçet's disease, chronic glomerulonephritis, chronic thrombocytopenic purpura,

autoimmune hemolytic anemia, migraine headache, stroke, subarachnoid hemorrhage, or a vasospasm in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI).

150. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, cardiovascular diseases, vasoconstriction, autoimmune disorders or vascular occlusive disorders in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI) and one or more agonists or antagonists of an Edg receptor.

151. A method for treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, cardiovascular diseases, vasoconstriction, autoimmune disorders or vascular occlusive disorders in a patient comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of structural formula (XXXI) and one or more drugs useful in treating or preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung diseases, surface epithelial cell injury, cardiovascular diseases, vasoconstriction, autoimmune disorders or vascular occlusive disorders.

152. The method of Claim 132 or 133, wherein the modulator is a compound of structural formula (XXXII):

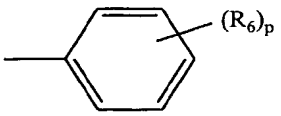


(XXXII)

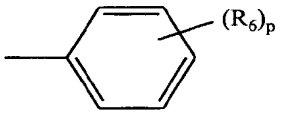
or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$,

-benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, -NH(aryl), -N=C(aryl), $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

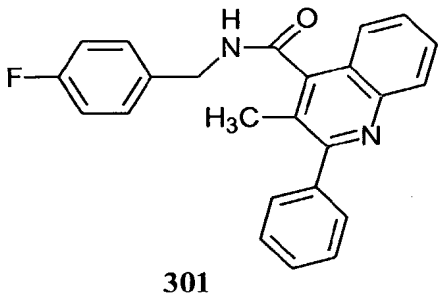
X is O, S, $C(R_5)(R_5)$ or $N(R_5)$;

R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

153. The method of Claim 132 or 133 wherein the modulator is selected from the group consisting of:



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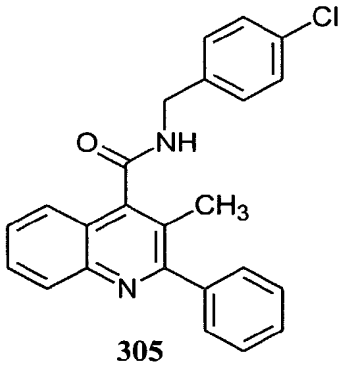
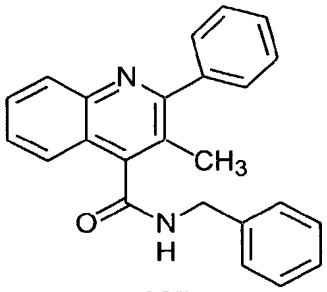


305



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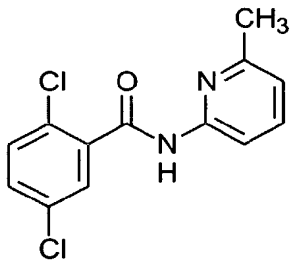

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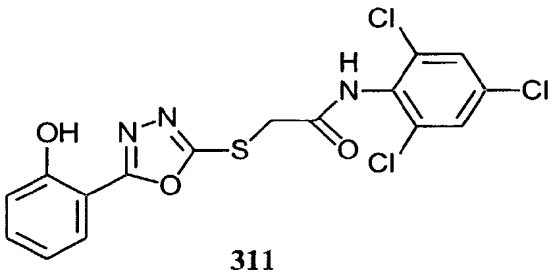
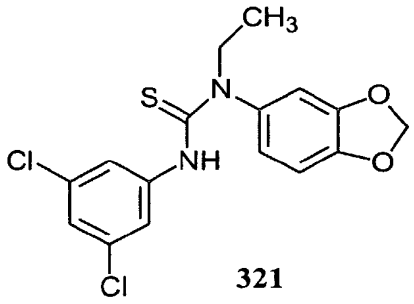
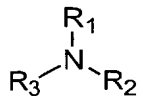


311



321

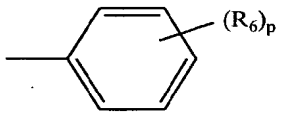
154. The method of Claim 132 or 133, wherein the modulator is a compound of structural formula (XXXIII):



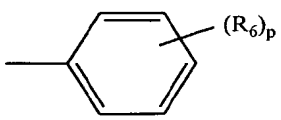
(XXXIII)

or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2 and R_3 is independently -H, -halo, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, $-C(S)N(R_5)(R_5)$, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



R_3 is -H $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -N=C(aryl), -heterocylcoalkyl, $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$,

-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl, -O(C_1-C_{10})alkyl, -C(O)(C_1-C_{10})alkyl, -C(O)NH(CH_2)$_m$(C_1-C_{10})alkyl, -OCF_3, -benzyl, -CO_2(CH_2)$_m$CH((C_1-C_{10})alkyl(C_1-C_{10})alkyl), -CO_2(C_1-C_{10})alkyl, -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$(C_1-C_{10})alkyl, -CO_2(CH_2)$_m$H, -NHC(O)(C_1-C_{10})alkyl, -NHC(O)NH(C_1-C_{10})alkyl, -NH(aryl), -N=C(aryl), -OC(O)O(C_1-C_{10})alkyl, or -SO_2NH_2;

X is O, S, or N(R_5);

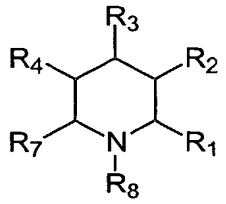
R_1, R_2 or R_3 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

155. The method of Claim 132 or 133, wherein the modulator is a compound of structural formula (XXXIV):

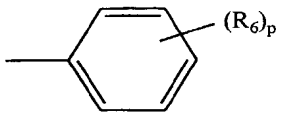


(XXXIV)

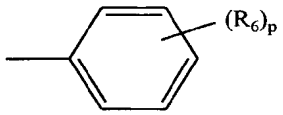
or a pharmaceutically available solvate or hydrate thereof, wherein;

each of R_1, R_2, R_3 R_4, R_7 and R_8 is independently -H, -halo, -NO_2, -CN, -C(R_5)$_3$, -(CH_2)$_m$OH, -N(R_5)(R_5), -O(CH_2)$_m$$R_5$, -C(O)$R_5$, -C(O)N$R_5$$R_5$, -C(O)NH($CH_2$)$_m$($R_5$), -$OCF_3$, -benzyl, -$CO_2$CH($R_5$)($R_5$), -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_5$)heteroaryl, -($C_6$)heteroaryl, -($C_5$-$C_{10}$)heteroaryl, -naphthyl, -(C_3-C_{10})heterocycle, -CO_2(CH_2)$_m$$R_5$, -N(OH)aryl, -NHC(O)$R_5$, -NHC(O)O$R_5$, -NHC(O)NH$R_5$, -heterocylcoalkyl, -C(S)N(R_5)(R_5), -(C_1-C_{10})alkylNHC(O)(CH_2)$_m$$R_5$, -($C_1$-$C_{10}$)alkylN$R_5$$R_5$,

-OC(O)$(CH_2)_m$CHR_5R_5, -$CO_2(CH_2)_m$CHR_5R_5, -OC(O)OR_5, -SR_5, -S(O)R_5, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



R_3 is -H -$C(R_5)_3$, -$(CH_2)_m$OH, -C(O)R_5, -C(O)NR_5R_5, -C(O)$NH(CH_2)_m(R_5)$, -benzyl, -CO_2CH$(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -$(C_5$-$C_{10})$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m R_5$, -N(OH)aryl, -NHC(O)R_5, -NHC(O)OR_5, -NHC(O)NHR_5, -N=C(aryl), -heterocylcoalkyl, -$(C_1$-$C_{10})$alkylNHC(O)$(CH_2)_m R_5$, -$(C_1$-$C_{10})$alkylNR_5R_5, -OC(O)$(CH_2)_m$CHR_5R_5, -$CO_2(CH_2)_m$CHR_5R_5, -OC(O)OR_5, -SR_5, -S(O)R_5, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



wherein;

each R_5 and R_6 is independently –H, -halo, -NO_2, -CN, -OH, -CO_2H, -N$(C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl, -O$(C_1$-$C_{10})$alkyl, -C(O)$(C_1$-$C_{10})$alkyl, -C(O)NH$(CH_2)_m(C_1$-$C_{10})$alkyl, -OCF_3, -benzyl, -$CO_2(CH_2)_m$CH$((C_1$-$C_{10})$alkyl$(C_1$-$C_{10})$alkyl), -$CO_2(C_1$-$C_{10})$alkyl, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, -$CO_2(CH_2)_m$H, -NHC(O)$(C_1$-$C_{10})$alkyl, -NHC(O)NH$(C_1$-$C_{10})$alkyl, -NH(aryl), -N=C(aryl), -OC(O)O$(C_1$-$C_{10})$alkyl, or -SO_2NH_2;

X is O, S, or N(R_5);

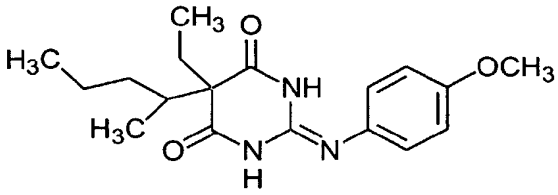
R_1 and R_2, R_2 and R_3, R_3 and R_4, R_4 and R_7, or R_7 and R_8 taken in combination can form one or more substituted or unsubstituted 5 or 6 membered cyclic or heterocyclic rings or a 6-membered aromatic ring;

two R_6 groups on adjacent carbon atoms can together form a 5 or 6 membered cyclic or heterocyclic ring or a 6-membered aromatic ring;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

156. The method of Claim 132 or 133 wherein the modulator has is selected from the group consisting of:



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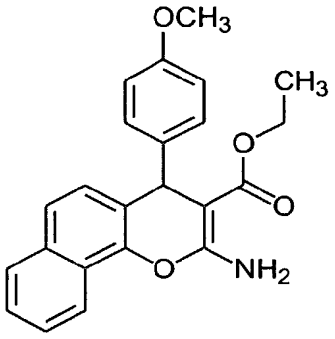
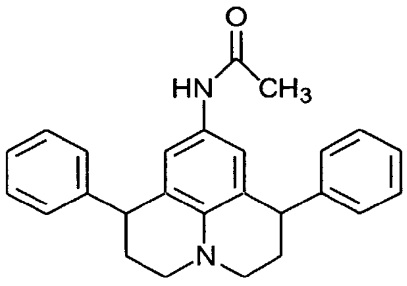
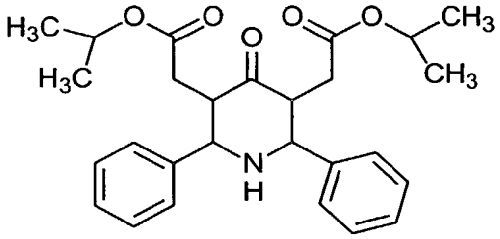


315



317



319

FIGURE 1

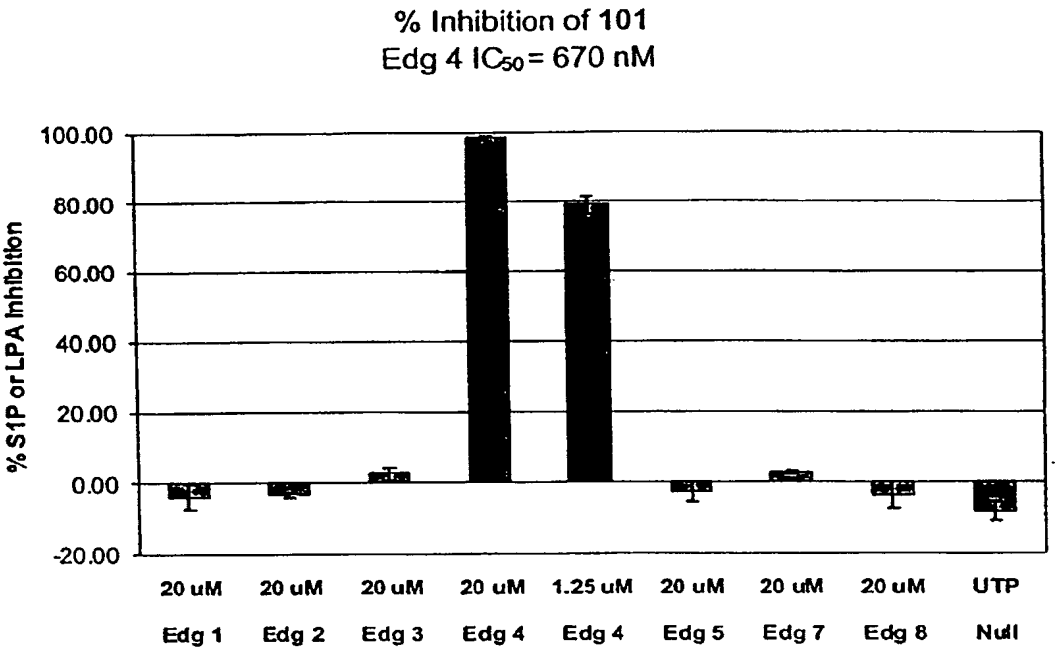

% Inhibition of 101
Edg 4 IC50 = 670 nM
% S1P or LPA Inhibition
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
20 uM Edg 1
20 uM Edg 2
20 uM Edg 3
20 uM Edg 4
1.25 uM Edg 4
20 uM Edg 5
20 uM Edg 7
20 uM Edg 8
UTP Null

FIGURE 2

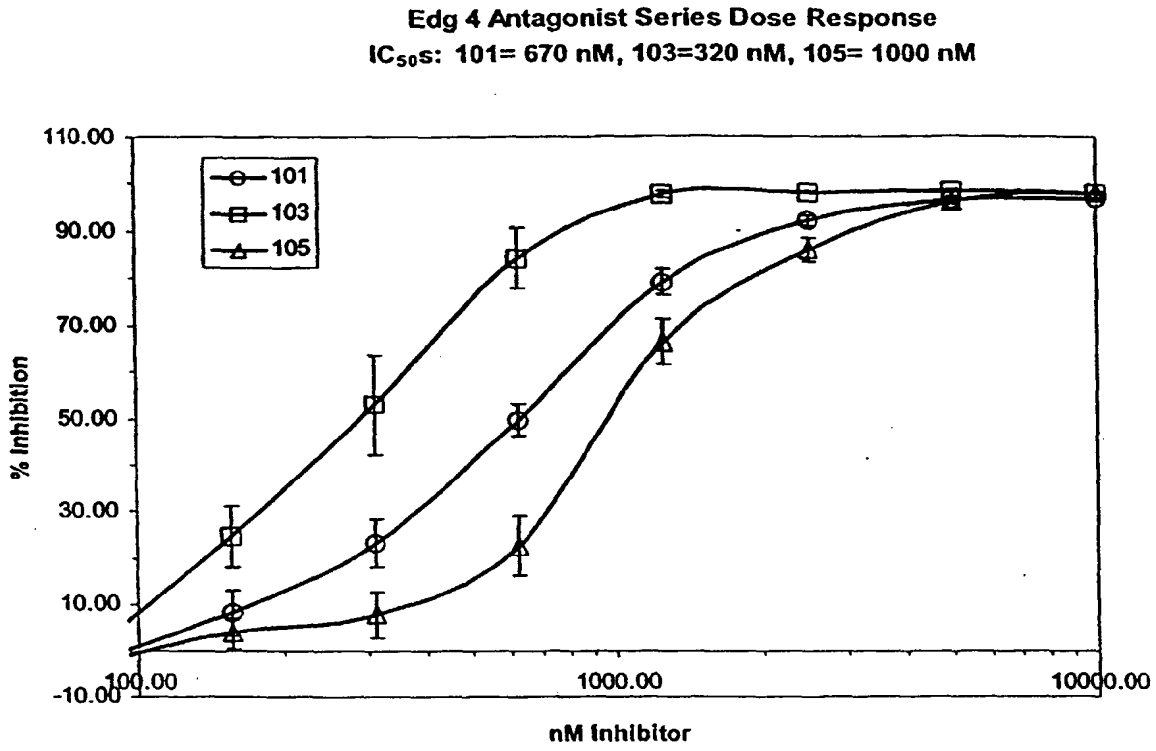

Edg 4 Antagonist Series Dose Response
IC50s: 101= 670 nM, 103=320 nM, 105= 1000 nM
110.00
90.00
70.00
50.00
30.00
10.00
-10.00
% Inhibition
101
103
105
100.00
1000.00
10000.00
nM Inhibitor

FIGURE 3

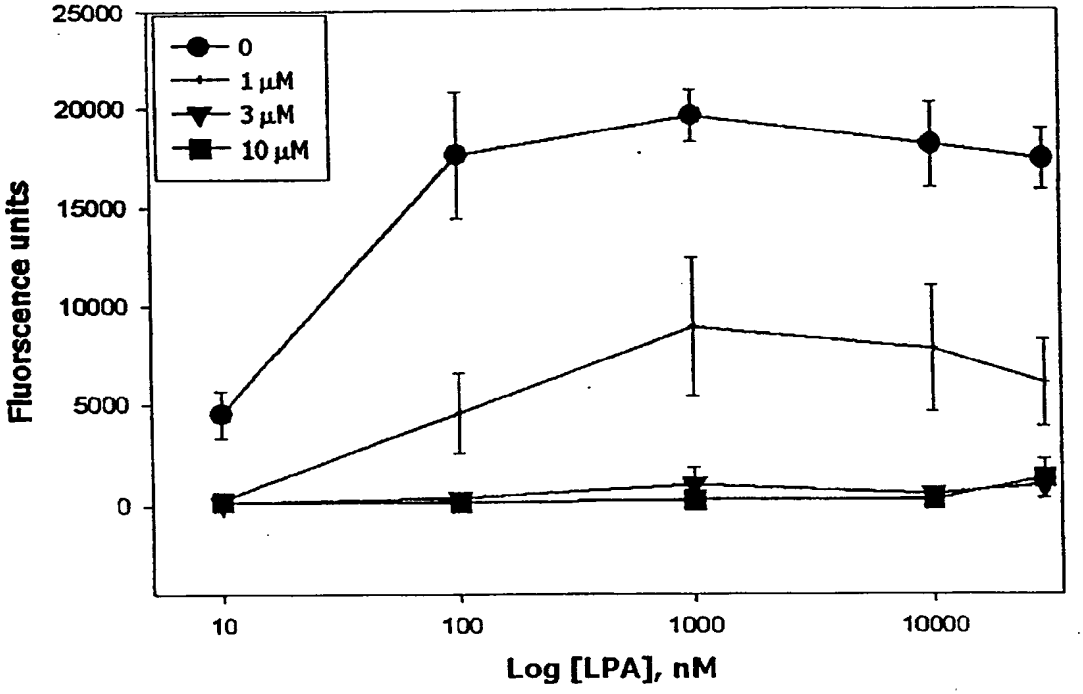

25000
20000
15000
10000
5000
0
Fluorscence units
0
1 µM
3 µM
10 µM
10
100
1000
10000
Log [LPA], nM

FIGURE 4

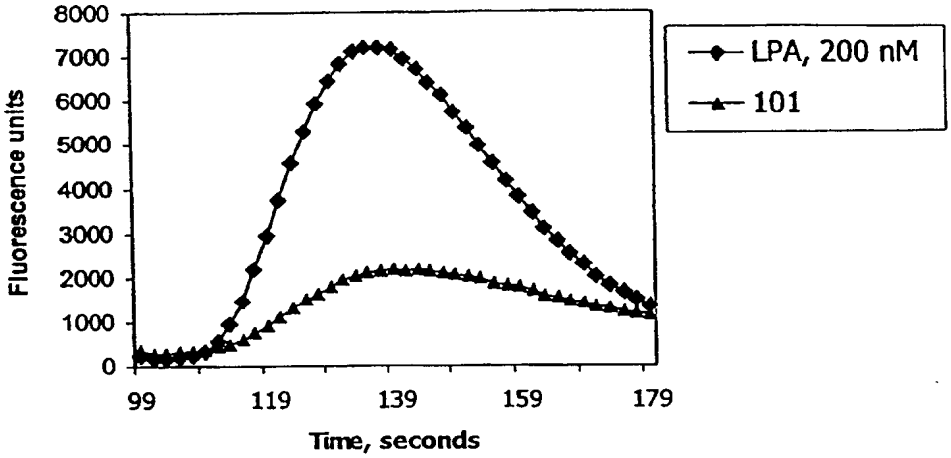

8000
7000
6000
5000
4000
3000
2000
1000
0
Fluorescence units
99
119
139
159
179
Time, seconds
LPA, 200 nM
101

FIGURE 5

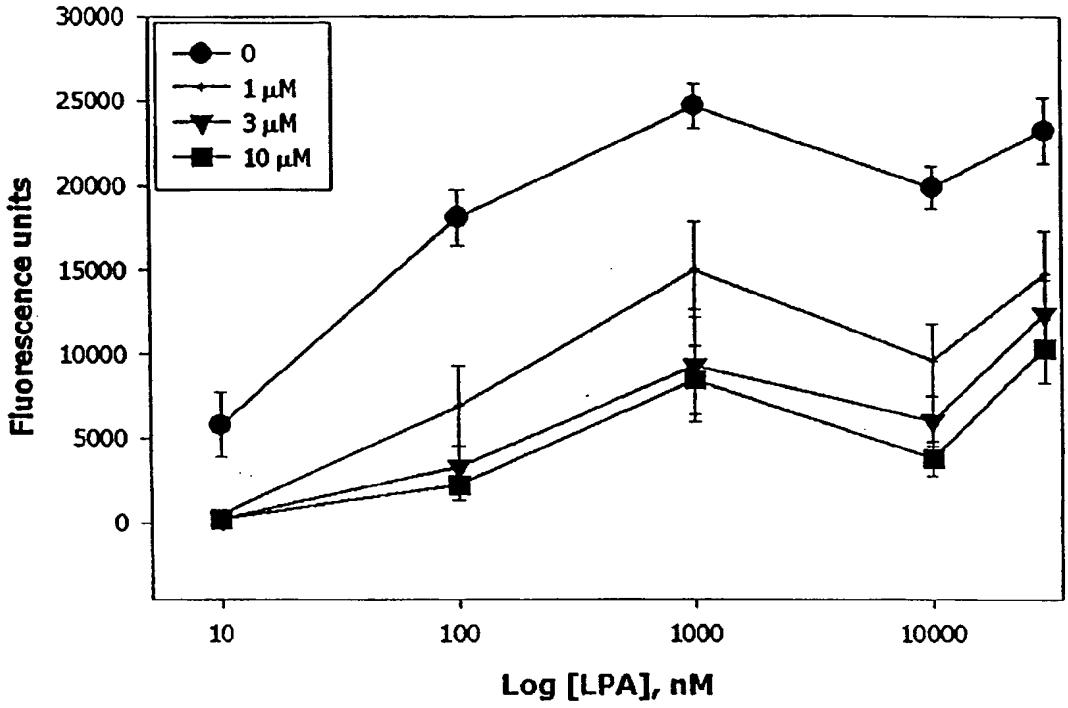

30000
25000
20000
15000
10000
5000
0
Fluorescence units
0
1 μM
3 μM
10 μM
10
100
1000
10000
Log [LPA], nM

FIGURE 6

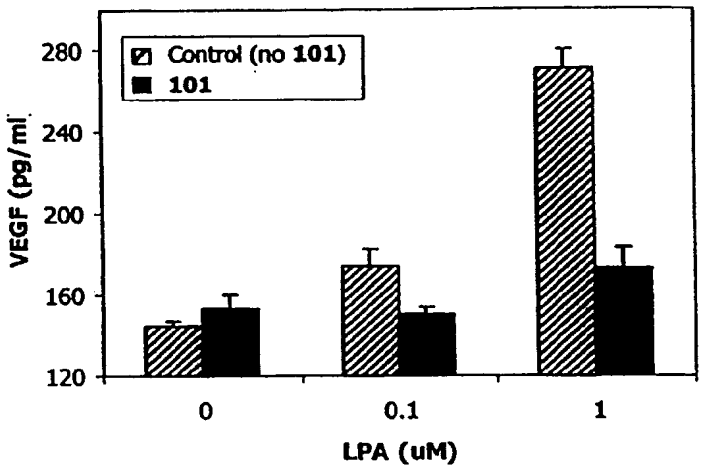


FIGURE 7

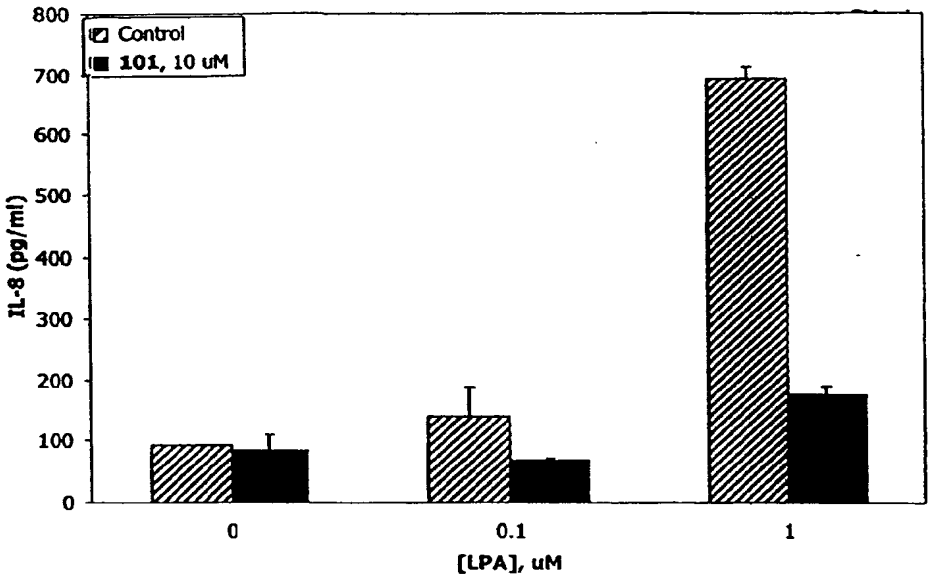

800
700
600
500
400
300
200
100
0
IL-8 (pg/ml)
Control
101, 10 uM
0
0.1
1
[LPA], uM

FIGURE 8

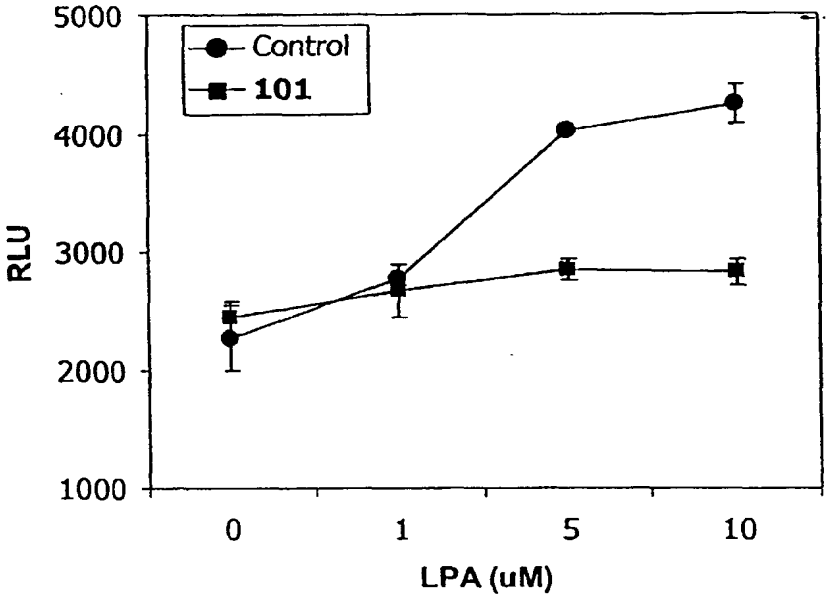


FIGURE 9

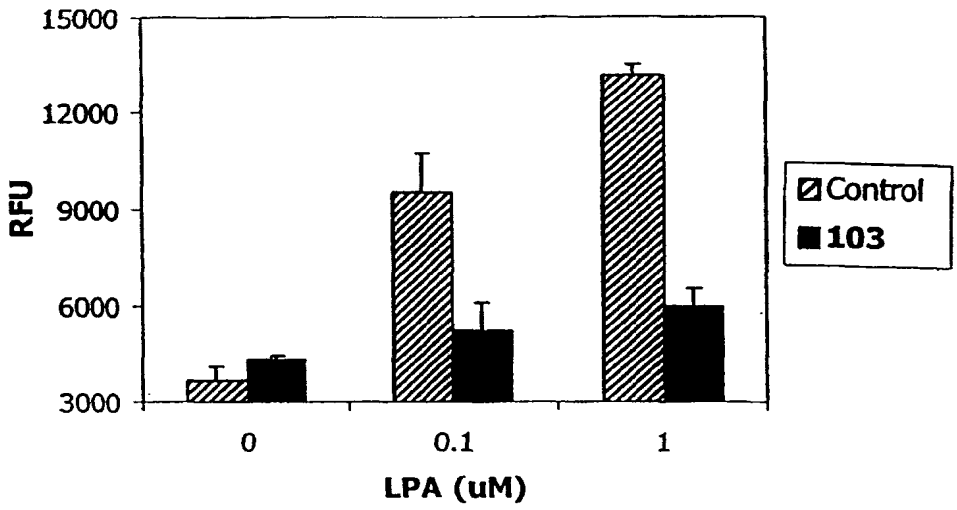
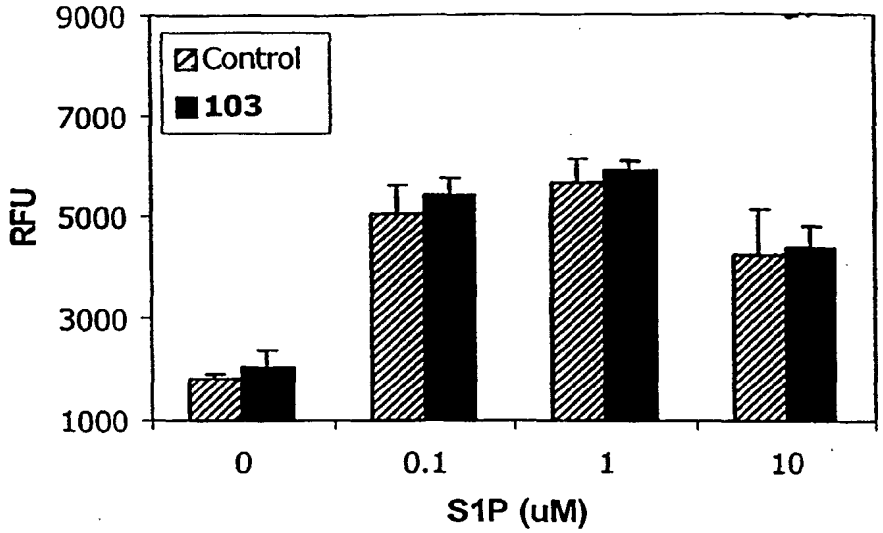


FIGURE 10



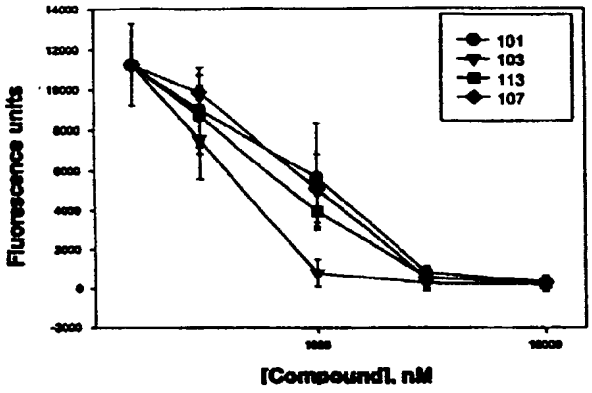


FIGURE 11

FIGURE 12

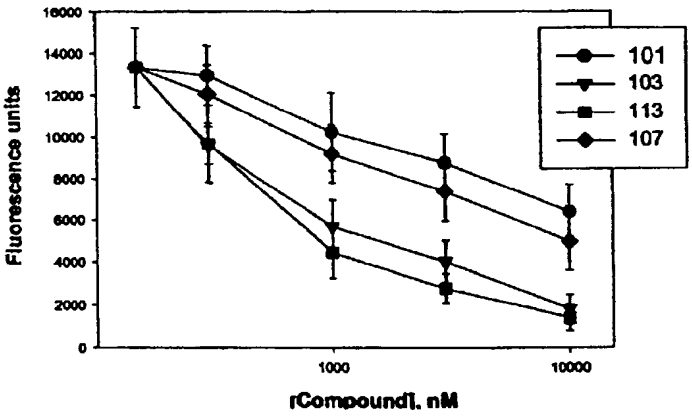

16000
14000
12000
10000
8000
6000
4000
2000
0
Fluorescence units
1000
10000
[Compound], nM
101
103
113
107

FIGURE 13

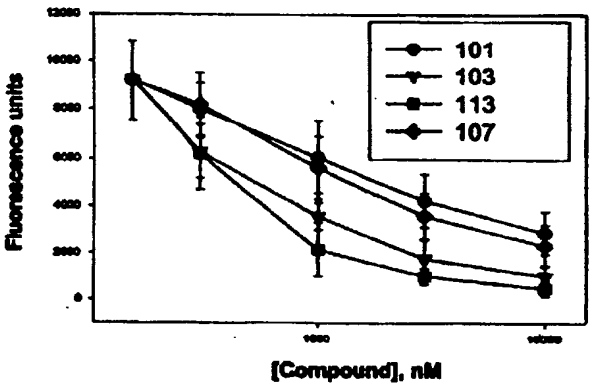


FIGURE 14

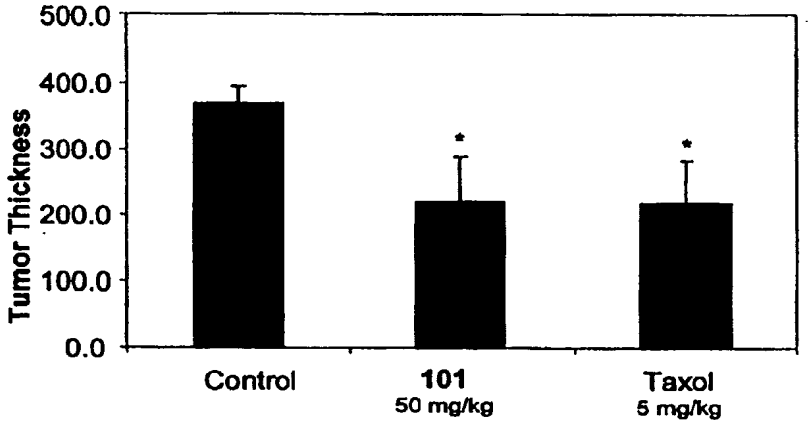

500.0
400.0
300.0
200.0
100.0
0.0
Tumor Thickness
*
*
Control
101
50 mg/kg
Taxol
5 mg/kg

FIGURE 15 Agonist 125 dose response in HTC E4 cells

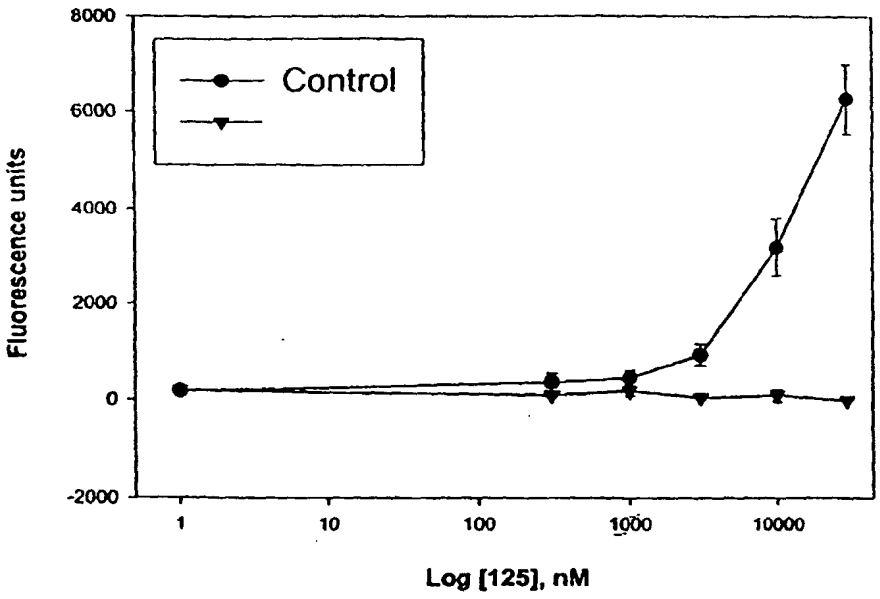


FIGURE 16 Agonist 125 dose response in CaOV-3 (human ovarian cancer) cells

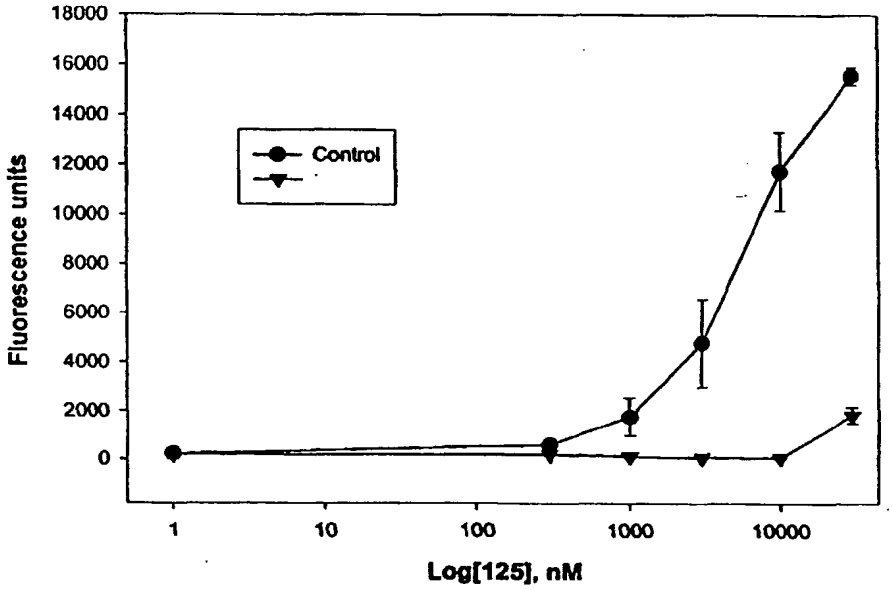


Figure 17
% Inhibition of 701
Edg 7 IC_{50}= 1.59μm

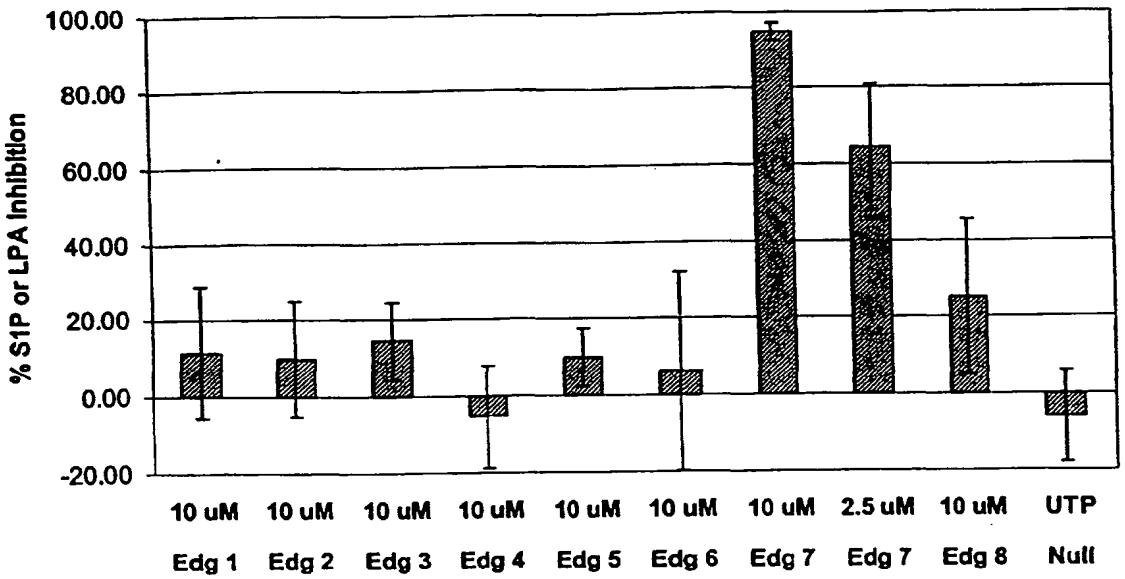


Figure 18
% Inhibition of 705
Edg 7 IC_{50}= 0.52μm

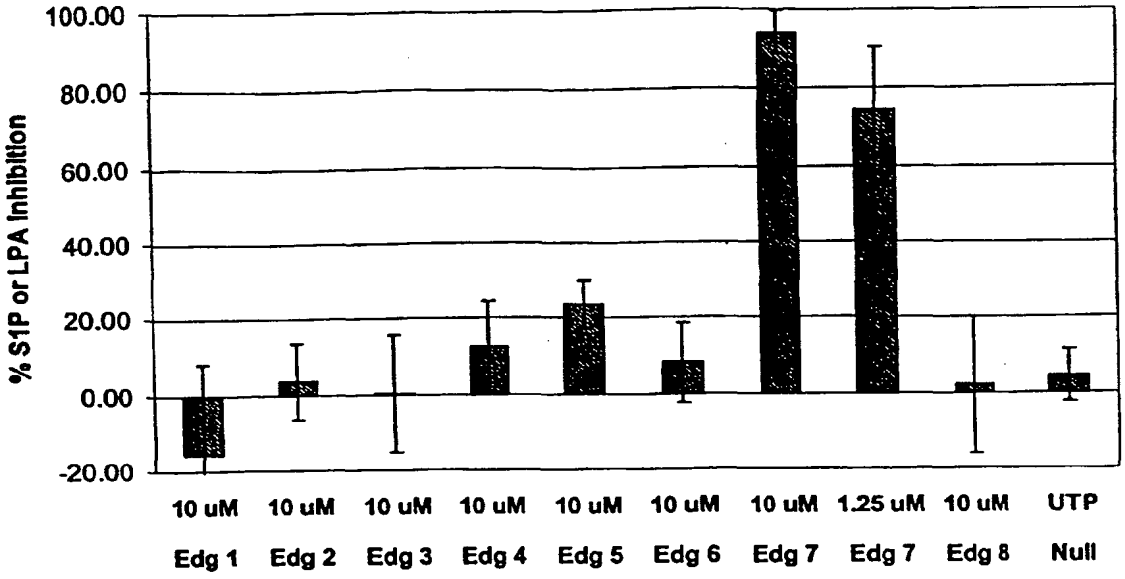


FIGURE 19

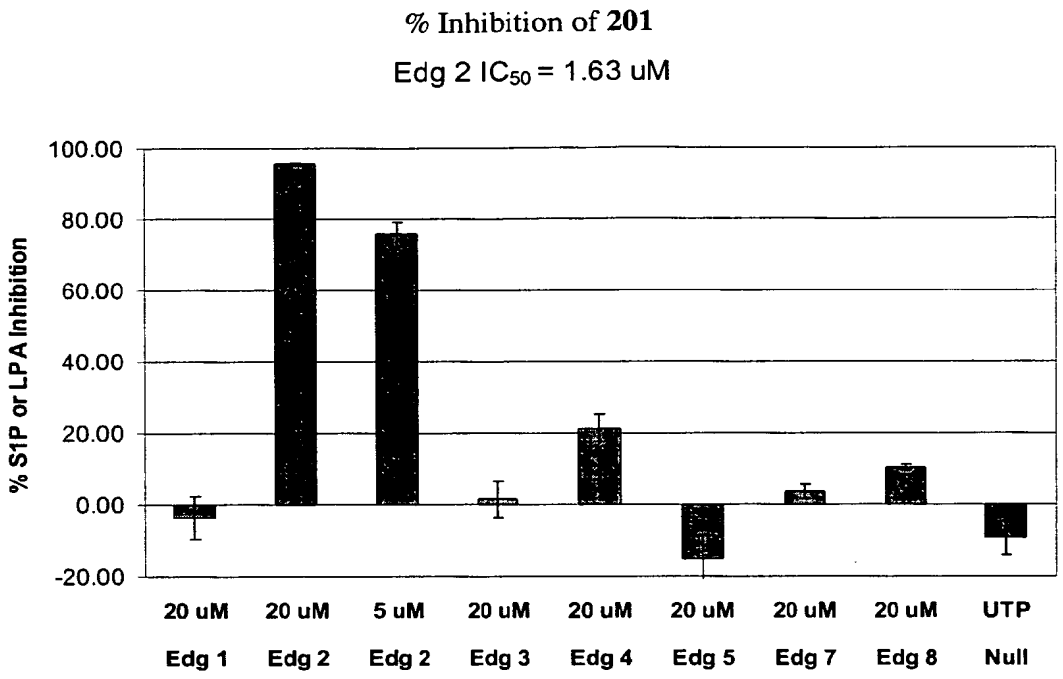

% Inhibition of 201
Edg 2 IC50 = 1.63 uM
% S1P or LPA Inhibition
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
20 uM Edg 1
20 uM Edg 2
5 uM Edg 2
20 uM Edg 3
20 uM Edg 4
20 uM Edg 5
20 uM Edg 7
20 uM Edg 8
UTP Null

FIGURE 20

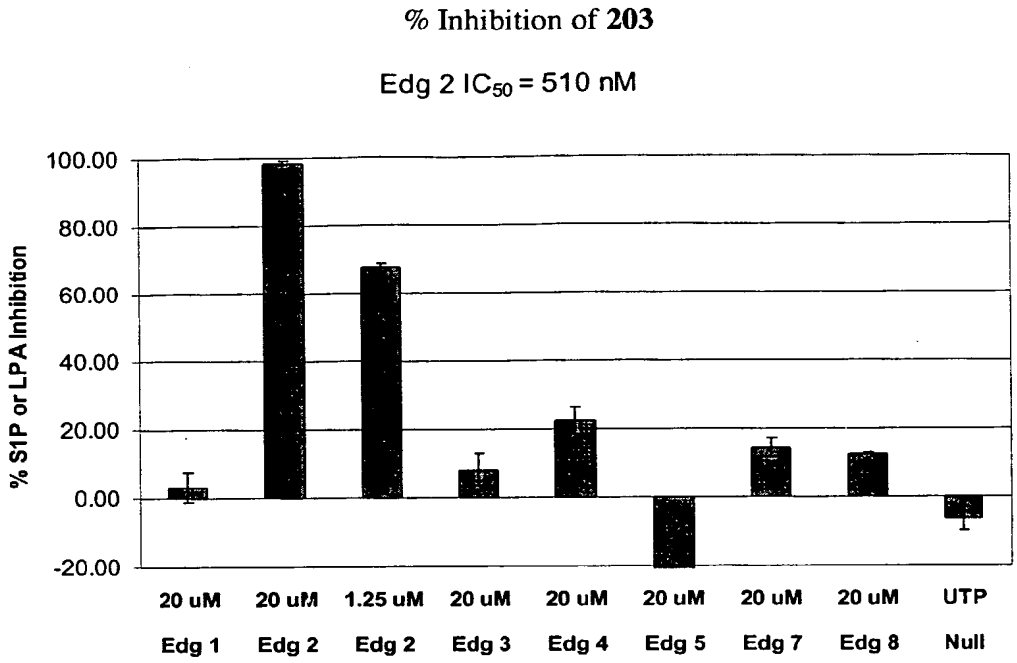

% Inhibition of 203
Edg 2 IC50 = 510 nM
% S1P or LPA Inhibition
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
20 uM Edg 1
20 uM Edg 2
1.25 uM Edg 2
20 uM Edg 3
20 uM Edg 4
20 uM Edg 5
20 uM Edg 7
20 uM Edg 8
UTP Null

FIGURE 21

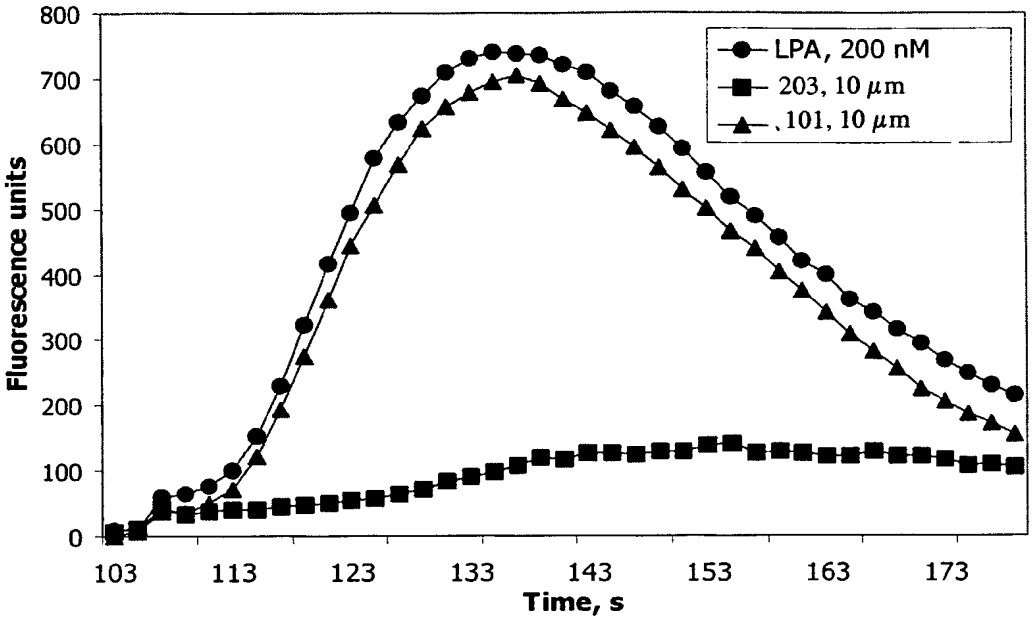

800
700
600
500
400
300
200
100
0
Fluorescence units
103
113
123
133
143
153
163
173
Time, s
LPA, 200 nM
203, 10 μm
101, 10 μm

FIGURE 22

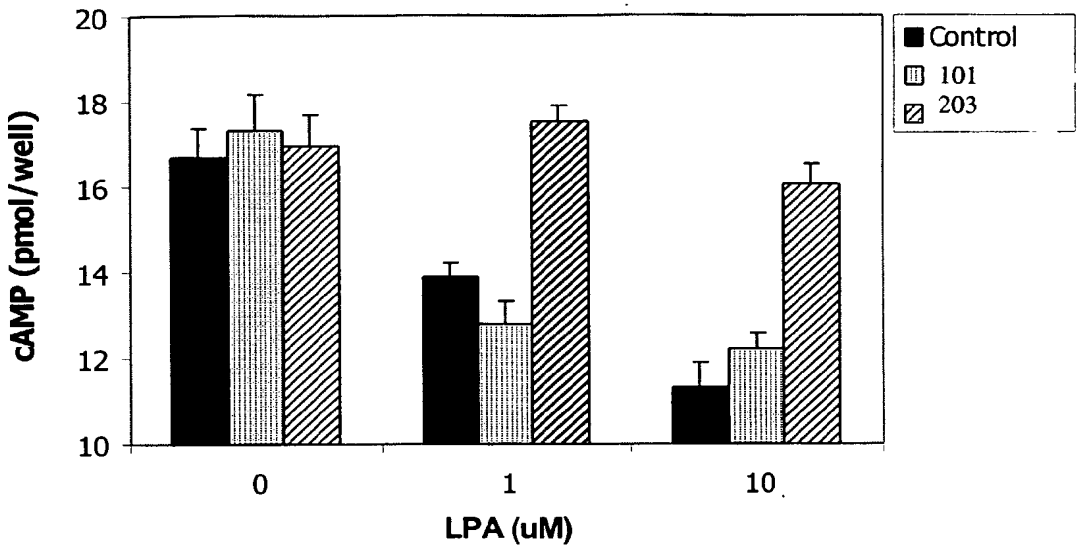


FIGURE 23

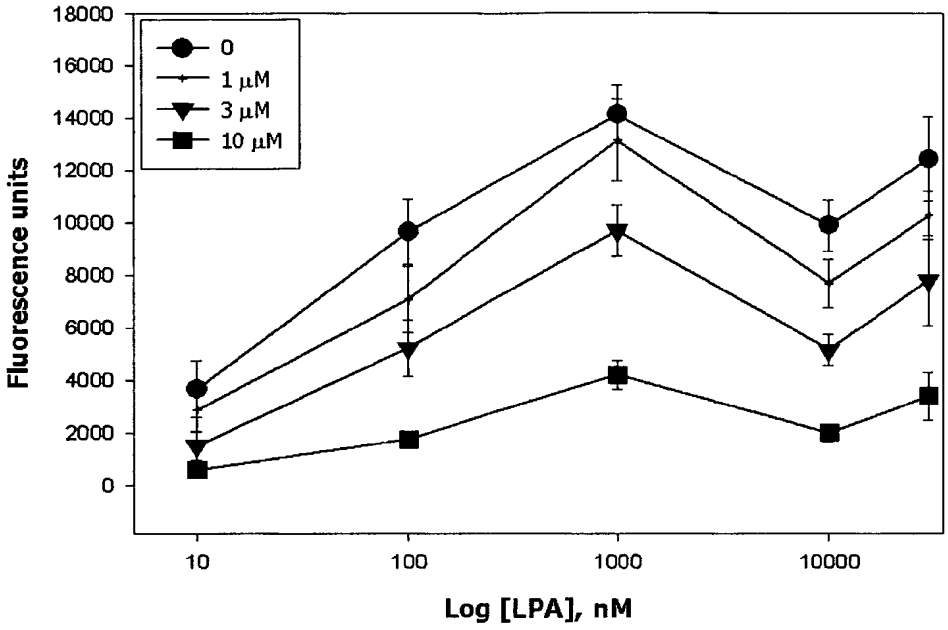

18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Fluorescence units
0
1 μM
3 μM
10 μM
10
100
1000
10000
Log [LPA], nM

FIGURE 24

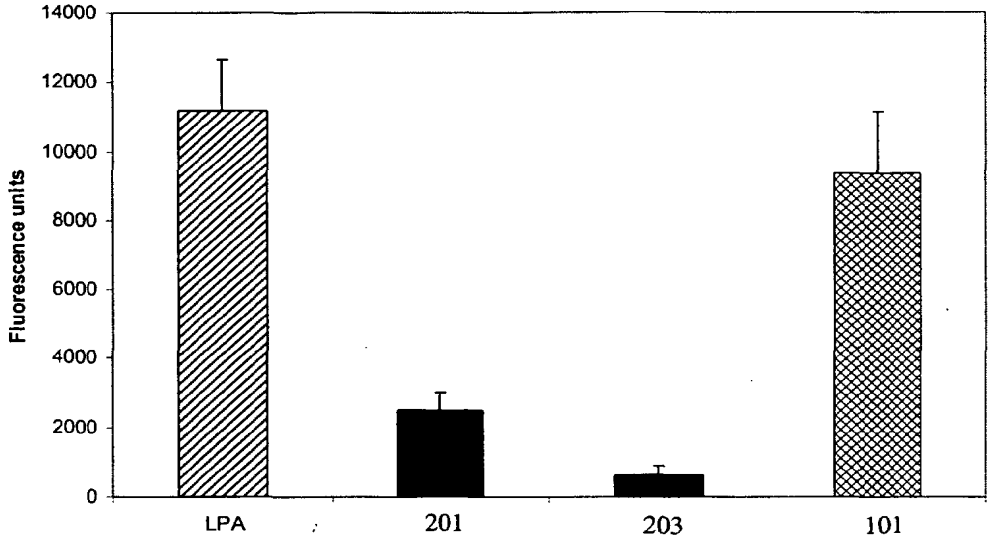

14000
12000
10000
8000
6000
4000
2000
0
Fluorescence units
LPA
201
203
101

TABLE 7

Selectivity of 301 for Edg-3

	301
Edg 1 IC_{50} μM	> 20
Edg 2 IC_{50} μM	> 20
Edg 3 IC_{50} μM	3.21
Edg 4 IC_{50} μM	> 20
Edg 5 IC_{50} μM	> 20
Edg 7 IC_{50} μM	> 20
Edg 8 IC_{50} μM	> 20
Fold Selective	**> 6.2**

TABLE 8

Pharmacology Profiling of 301

Adrenergic
Alpha 1, non-selective
Alpha 2, non-selective
Beta, non-selective
Calcium Channels
Type L, DHP
Dopamine
D2L
Endothelin
ETA
H1 central
Muscarinic, non-selective, central
Serotonin
5HT1 non-selective
Angiotensin AT2

TABLE 8

Pharmacology Profiling of 301

Adrenergic
Alpha 1, non-selective
Alpha 2, non-selective
Beta, non-selective
Bradykinin
B1
B2
Calcium Channels
Type L, DHP
Type L, BTP
Type L, PAA
Type N
Dopamine
D2L
CB2
Chemokine
CCR1
CCR2B
CCR4
CCR5
IL-8, non selective
Dopamine
D1
D2L
D2S
D3
D4.2
D4.4
D4.7
D5
Endothelin
ETA
ETB
EGF
Histamine
H1 central
H1 peripheral
H2
H3
Imidazoline
I2, central
I2, peripheral

Muscarinic
M1
M2
M3
M4
M5
Muscarinic, non-selective, central
M, Oxotremorine-M
NPY
NPY 1
NPY2
Nicotninc ACh, Central
Opiate, non-selective
PAF
PDGF
Prostanoid
EP1
EP4
Purinergic
P2X
P2Y
Serotonin
5HT1 non-selective
5HT2
5HT2A
5HT2B
5HT2C
5HT3
5HT4
5HT5A
5HT6
5HT7
Sigma, non-selective
Sodium Channel
Site 1
Site 2
Tachykinin
NK1
NK2
NK3
TGF
TNF
VEGF
VIP1
Angiotensin AT2

FIGURE 25

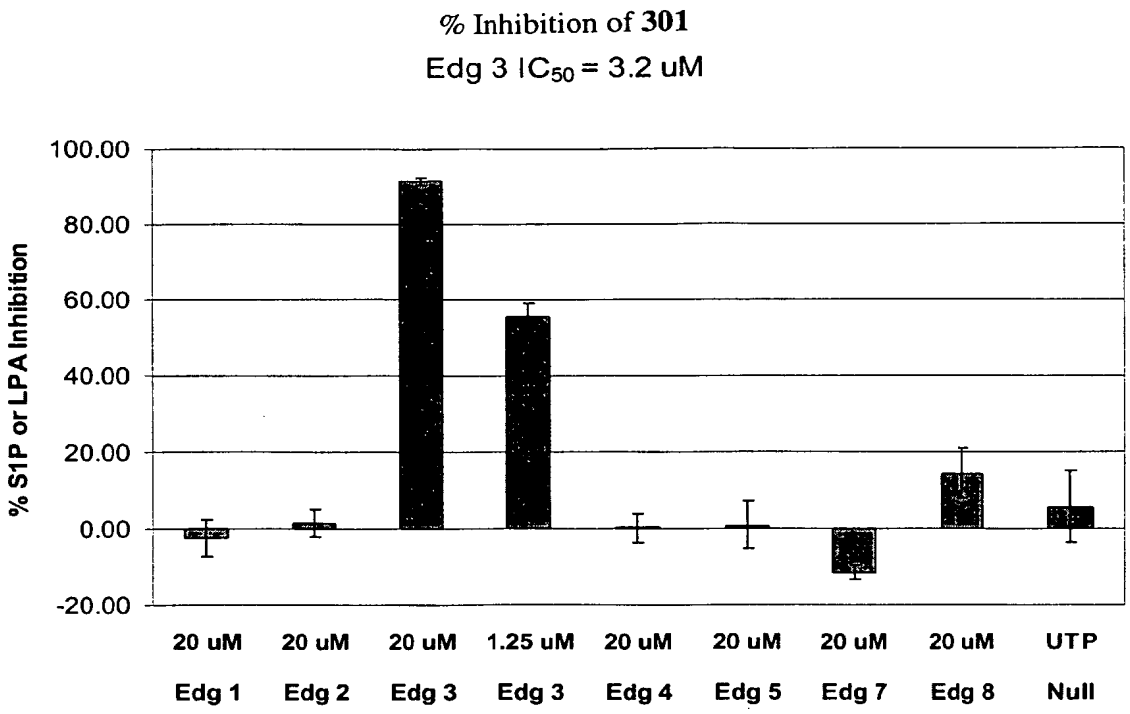

% Inhibition of 301
Edg 3 IC50 = 3.2 uM
% S1P or LPA Inhibition
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
20 uM Edg 1
20 uM Edg 2
20 uM Edg 3
1.25 uM Edg 3
20 uM Edg 4
20 uM Edg 5
20 uM Edg 7
20 uM Edg 8
UTP Null

FIGURE 26

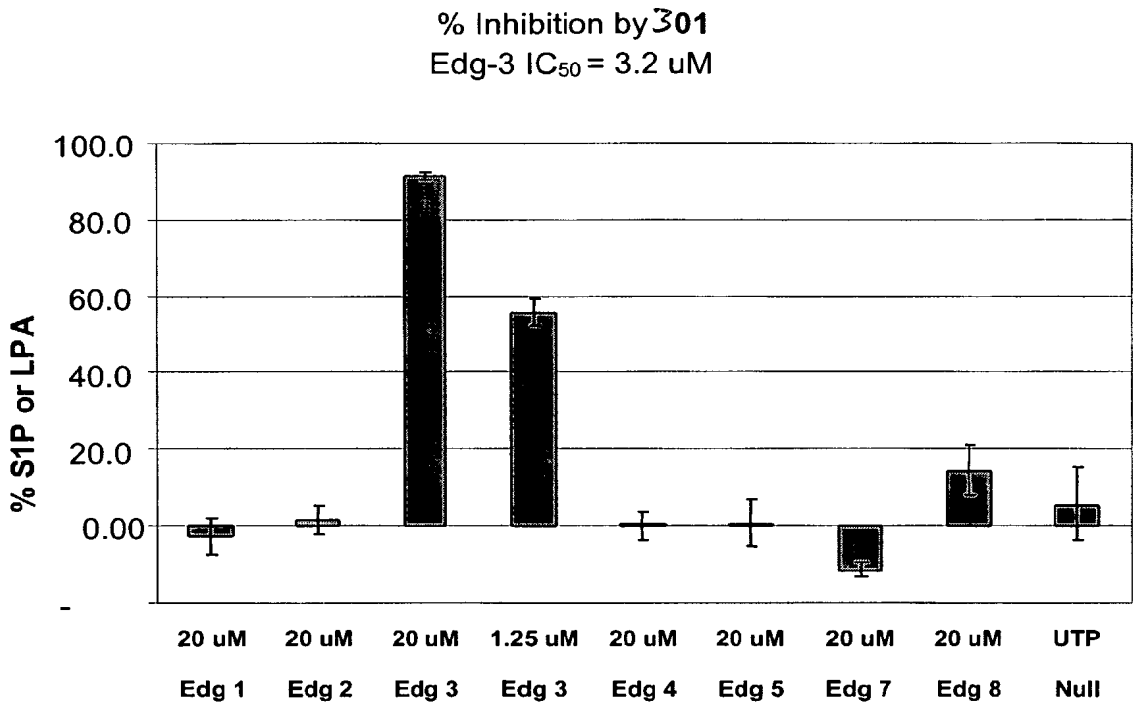

% Inhibition by 301
Edg-3 IC50 = 3.2 uM
100.0
80.0
60.0
40.0
20.0
0.00
-
% S1P or LPA
20 uM Edg 1
20 uM Edg 2
20 uM Edg 3
1.25 uM Edg 3
20 uM Edg 4
20 uM Edg 5
20 uM Edg 7
20 uM Edg 8
UTP Null

Table 3

Selectivity of 701, 705 and 707 for Edg-7

	101	105	107
Edg 1 IC_{50} μM	>20	>20	>20
Edg 2 IC_{50} μM	>20	>20	>20
Edg 3 IC_{50} μM	>20	>20	>20
Edg 4 IC_{50} μM	>20	>20	>20
Edg 5 IC_{50} μM	>20	>20	>20
Edg 6 IC_{50} μM	>20	>20	>20
Edg 7 IC_{50} μM	1.59	0.52	7.73
Edg 8 IC_{50} μM	>20	>20	>20
Fold Selectivity	>12.6	>38.5	>2.6

Table 4

Selectivity of Edg-7 Agonists 727, 729 and 733

	127	129	133
Edg 1 EC_{50} μM	>25	>25	>25
Edg 2 EC_{50} μM	>25	>25	>25
Edg 3 EC_{50} μM	>25	>25	>25
Edg 4 EC_{50} μM	>25	>25	>25
Edg 5 EC_{50} μM	>25	>25	>25
Edg 6 EC_{50} μM	>25	>25	>25
Edg 7 EC_{50} μM	0.23	0.37	1.61
Edg 8 EC_{50} μM	>25	>25	>25
Null EC_{50} μM	>25	>25	>25
Fold Selectivity	>109	>68	>15.5

TABLE 5

Selectivity of 201 and 203 for Edg-2

	201	203
Edg 1 IC_{50} μM	> 20	> 20
Edg 2 IC_{50} μM	1.63	0.51
Edg 3 IC_{50} μM	> 20	> 20
Edg 4 IC_{50} μM	> 20	> 20
Edg 5 IC_{50} μM	> 20	> 20
Edg 7 IC_{50} μM	> 20	> 20
Edg 8 IC_{50} μM	> 20	> 20
Fold Selective	**> 12.3**	**> 39.3**

TABLE 6

Pharmacology Profiling of 201

Adrenergic
Alpha 1, non-selective
Alpha 2, non-selective
Beta, non-selective
Calcium Channels
Type L, DHP
Dopamine
D2L
Endothelin
ETA
H1 central
Muscarinic, non-selective, central
Serotonin
5HT1 non-selective
Angiotensin AT2

TABLE 6

Pharmacology Profiling of 201

Adrenergic
Alpha 1, non-selective
Alpha 2, non-selective
Beta, non-selective
Bradykinin
B1
B2
Calcium Channels
Type L, DHP
Type L, BTP
Type L, PAA
Type N
Dopamine
D2L
CB2
Chemokine
CCR1
CCR2B
CCR4
CCR5
IL-8, non selective
Dopamine
D1
D2L
D2S
D3
D4.2
D4.4
D4.7
D5
Endothelin
ETA
ETB
EGF
Histamine
H1 central
H1 peripheral
H2
H3
Imidazoline
I2, central
I2, peripheral

Muscarinic
M1
M2
M3
M4
M5
Muscarinic, non-selective, central
M, Oxotremorine-M
NPY
NPY 1
NPY2
Nicotninc ACh, Central
Opiate, non-selective
PAF
PDGF
Prostanoid
EP1
EP4
Purinergic
P2X
P2Y
Serotonin
5HT1 non-selective
5HT2
5HT2A
5HT2B
5HT2C
5HT3
5HT4
5HT5A
5HT6
5HT7
Sigma, non-selective
Sodium Channel
Site 1
Site 2
Tachykinin
NK1
NK2
NK3
TGF
TNF
VEGF
VIP1
Angiotensin AT2